COLD INJURY

Transactions of the First Conference

June 4 5 1951 New York, New York

Edited by

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DEPARTMENT OF MEDICINE
COLLEGE OF PHYSICIANS AND SURGEONS
COLUMBIA UNIVERSITY
NEW YORK, NEW YORK

Sponsored by the

JOSIAH MACY JR. FOUNDATION

565 PARK AVENUE, NEW YORK 1 N. Y

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Price $3.25

Printed in the United States of America
By The Hildreth Press Inc Bristol Connecticut

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First Conference on Cold Injury

JOSIAH MACY JR FOUNDATION CONFERENCE PROGRAM

FRANK FREMONT SMITH M D
Medical Director

As an introduction to these Transactions of the First Conference on Cold Injury I should like to outline what it is that the Foundation hopes to accomplish by its Conference Program. We are interested, first of all, in furthering knowledge about cold injury and to this end the participants were brought together to exchange ideas experiences, data, and methods. In addition to this particular goal however there is a further and perhaps more fundamental, aim which is shared by all our conference groups. This is the promotion of meaningful communication between scientific disciplines

The problem of communication between disciplines we feel to be a very real and a very urgent one the most effective advancement of the whole of science being to a large extent dependent upon it Because of the accelerating rate at which new knowledge is accumulating and because discoveries in one field so often result from information gained in quite another channels must be established for the most relevant dissemination of this knowledge

The increasing realization that nature itself recognizes no boundaries makes it evident also that the continued isolation of the several branches of science is a serious obstacle to scientific progress Particularly is it so in medicine that the limited view through the lens of one discipline is no longer enough For example today medicine must be well versed in nuclear physics because of the tracer techniques and the injury which can result from radiation At the other extreme, medicine is certainly a social science and, through mental health, must be concerned with economic and social questions The answer then, is not further fragmentation into increasingly isolated specialties disciplines, and departments, but the integration of science and scientific knowledge for the enrichment of all branches. This integration, we feel can be encouraged by providing opportunities for a multiprofessional approach to given topics

Although the fertility of the multidiscipline approach is recognized adequate provision is not made for it by our universities, scientific societies, and journals And perhaps the presence of other hindering factors must be admitted Partly semantic in nature, they may also to some degree be psychological Admittedly it is oftentimes difficult to accept data derived from methods with which one is unfamiliar By making free and informal discussion the central core of our meetings, we hope to achieve an atmosphere which minimizes as much as possible these emotional barriers

Thus our meetings are in contrast to the usual scientific gatherings. They are not designed to present neat solutions to tidy problems but to elicit provocative discussion of the difficulties which are being encountered in research and practice. For this reason, we ask that the presentations be relatively brief and that emphasis be placed on discussion as the heart of the meeting Our hope is that the participants will come prepared not to defend a single point of view but to take advantage of the meeting as an opportunity to speak with representatives of other disciplines in much the same way that they would talk with their colleagues in their own laboratories

We have, now thirteen groups functioning under the Conference Program, and the following topics are covered adrenal cortex, aging, blood clotting cold injury connective tissues, consciousness, cybernetics, infancy and childhood liver injury metabolic interrelations, nerve impulse renal function, and shock and circulatory homeostasis.

When a new conference is organized, the Chairman in consultation with the Foundation selects fifteen scientists to be the nucleus of the group and every effort is made to include representatives from all pertinent disciplines From time to time new members are added by the group to fill gaps in viewpoint or technique. A limited number of guests are invited to attend each meeting, but, for the purpose of promoting full participation by all members and guests, attendance at any meeting is limited to twenty-five It is inevitable that in no topic can we possibly include more than a small fraction of the key investigators in the field and one of the difficulties in forming a group like this is the necessity to leave out so many people whom we would like to include

The transactions of these meetings are recorded and published This is done because the Foundation wishes to make current thinking in a field available to all those working in it and because it believes that conveying to those in other fields who are concerned with science for example government officials, administrators, etc., the essential nature of scientific research is also an important problem in communication Logic is a vital aspect of science, but equally essential is the intuitive or creative aspect. Research is as creative as the painting of a portrait or the composing of a symphony Although logic is, of course, necessary in order to rearrange to test, and to validate, research thrives on creativity which has its source in unconscious, nonrational processes Unfortunately however in the finished products which are presented to the world through research reports this integral part of scientific endeavor is shriveled by the cold, white light of logic. By preserving the informality of our conferences in the published transactions, we hope to give a truer picture of what actually goes on in the minds of scientists and of the role which creativity plays.

INTRODUCTORY REMARKS

Talbott Before I make the few remarks that a chairman considers pertinent in introducing a discussion group such as this I should like to have each one stand up and tell us his university institutional, or Armed Forces affiliation, and three or four sentences to indicate his interest in cold.

In selecting this discussion group, an effort was made, and successfully so, to have representatives from the Armed Forces, the Army the Navy and the Air Forces in this country We hope to have two representatives from England Actually we have one. Dr Ungley who was scheduled to come, was unable to do so at the last moment There are two representatives from Canada, and we may yet have a third one Dr Bigelow has promised to come if possible. It is of interest that we have physiologists, biophysicists, surgeons, and internists present

Dr Crismon will now tell us about his interest in cold.

JEFFERSON M CRISMON: I am from the Department of Physiology Stanford University The first work that we did on cold was a study of hypothermia in 1940 1941 and 1942 From results obtained in that study we became interested in carrying out further work on regional cold injury Our studies on gangrene caused by frostbite occupied a one year program between 1944 and 1945 under Office of Scientific Research and Development support. Since that time we have done nothing else with cold injury per se but our present research has grown out of the frostbite study We felt that we wanted to know more about the metabolic consequences of ischemia and the problems of control of blood flow in small vessels.

EDWARD A. SELLERS: I am from the Department of Physiology the University of Toronto During the war I became interested in physiological problems concerned with heat, but after the war a sudden transformation took place, and the Defense Research Board of Canada has been supporting me in a study of physiological and pharmacological changes caused by cold A good deal of our work has involved exposing small animals, especially rats, for prolonged periods to moderate degrees of cold (just about

perience, a task which has not yet been completed I find, how ever that the Air Force has done an admirable job in summarizing a great deal of the experimental work in Germany in the two volumes covering German Aviation Medicine in World War II. However in summary I can say that I was contemplating whether or not in this confused subject as in vibration or burns, there were not some guiding principles stemming from basic studies. More immediately important to the military are the principles of therapy which might be summarized to guide internists and surgeons and especially individuals in the battle line, the men themselves, so that some of the gruesome results that have occurred in Europe as a result of faulty treatment will not be repeated in our forces

JEROME W CONN I am in the Department of Medicine, University of Michigan, Ann Arbor I am primarily an internist with an interest in the physiology of normal and abnormal conditions of man. Frankly I know nothing about cold or cold injury When I was invited to be a member of this Conference, I told Dr Talbott that I thought I would have very little to offer to this group and that I felt that I probably didn t belong with it. But Dr Talbott said he would like to have a person from the Macy Conference on Adrenal Cortex of which I am a member represented here, and so I accepted.

JOSEPH R. BLAIR: I am from the Army Medical Research Laboratory at Fort Knox, Kentucky I have been interested in the physiological and pathological aspects of cold exposure for the past five years. During that time I spent two winters in the Arctic with Dr Gottschalk, and this past winter I had the good fortune of accompanying Dr Talbott and Dr Gottschalk to Japan and Korea to study cold injuries there At present I am a member of the Environmental Medicine Branch of the Army Medical Research Laboratory We are interested both in animal and in human studies on the effects of cold

ROBERT KARK: I am a physician a practicing internist. I am from the Department of Medicine of the University of Illinois. My main, interests cover the metabolic and nutritional aspects of disease in man. In 1941 I was pushed into a cold chamber by Dr Burton and the late Dr Barett when I was in the Canadian Air Force, and from there on, somehow or other I got mixed up with cold and hot climates in relation to military activities, in places like the Arctic, Northwest Canada, and Burma. My particular hobby

in medicine is the relation of climate to disease, both in producing disease and in modifying disease states

GEORGE E. BURCH I am from the Department of Medicine at Tulane University My interest has been in the cardiovascular system, and particularly in the influence of tropical and subtropical environments on this system. During the war the Office of Scientific Research and Development, in association with the Army asked that I become interested in the study of trench foot. During the course of the study the war ended, which concluded the project. We then returned to our problems on hot and warm climates, and became interested in the use of radioactive elements in the study of turnover of electrolytes We were curious about the rates at which electrolytes found their way into sweat, and the relationship of the variations with time in concentrations in sweat, urine, and blood Our experiments have continued along these general lines More recently in association with C. T Ray a program is in progress for the National Research Council to follow up trench-foot casualties from the last war At the moment that is the only type of our research that is directly related to cold.

STEVEN M. HORVATH I am from the Department of Physiology State University of Iowa. My interest in this particular problem began at the Fatigue Laboratory where we were interested in the problems of stress, and I had an opportunity to work with Dr Talbott on some hypothermia experiments Then I went on to the Armored Medical Research Laboratory which is now the Army Medical Research Laboratory where we were again interested in environmental problems partially in heat and partially in cold From there I went into physical medicine, and again the problems were related to heat and cold Now I have moved to Iowa where we are continuing in this particular type of work but I am slightly more interested in the peripheral circulation than I am in just temperature regulation.

PAUL A. SIPLE I am from the Department of the Army General Staff Research and Development Division, in charge of the Environmental Research Division and chairman of the Department of Army's Environmental Factor and Control Committee. I am a geographer and climatologist therefore my primary interest is concerned with the preventive-medicine aspects and the environment under which cold injuries occur

My personal experience has included several years in the polar regions, particularly the Antarctic, and I therefore have had a

direct personal interest in cold and its effect on man for quite a number of years. During the war I was sent to the European theater of operation on a special mission to investigate the trench-foot situation and the cause of it. I have continued active interest in the field of protective devices, clothing, footwear and so on, in regard to prevention of cold injuries In addition to my regular work with the Army related to these fields, I have been carrying on research in my own laboratory particularly that which is related to environmental factors fabrics, and thermal-transfer phenomena.

HARRIS B SCHUMACKER JR.: I am from the Indiana University School of Medicine I am a surgeon who has a particular interest in cardiovascular surgery Though I had previously been somewhat interested in the injuries resulting from cold and especially in their vasomotor sequelae a more intense concern with these injuries developed during World War II At that time I had the good fortune to direct one of the Army s three vascular centers in which were hospitalized most of those soldiers who as the result of injury or disease, had vascular problems which required special personnel and facilities for their proper study and treatment. As a result of this experience, which included the management of hundreds suffering from the various cold injuries, I was impressed with the magnitude of the problem. It struck me as a disheartening and provoking fact that practically no progress had been made between the two world wars with regard to understanding the cold injuries, preventing them, or treating them. I resolved then that, once the war was over I would try to find out something more about them and since the war there has been going on in my laboratory a fairly active program of research in frostbite.

JOHN H TALBOTT Dr Fremont Smith said that I should say a word about myself

My interest in cold precedes the Second World War In the late thirties we completed a series of studies on hypothermia in human beings More will be said about this work tomorrow morning During the Second World War I was stationed for a time at the Climatic Research Laboratory on loan from the Surgeon General of the Army to the Quartermaster General In that laboratory there were cold chambers as well as hot chambers. Recently I was a member of a mission sent to the Far East Command to study the frostbite problem in Korea and Japan. Other members of this mission were Colonel Blair and Dr Gottschalk.

FRANK FREMONT SMITH: My interest in cold goes back to college days when I used to take cold plunges in the bathtub. It was during the process of lowering myself into cold water in the early morning that I learned something about the problems of hyperventilation under such circumstances.

On a very hot day at the Massachusetts General Hospital some years later I had myself lowered on a sheet, without clothing, into a huge tub which had ice floating around in it. Attached to me was a basal metabolic machine to measure respiration. Also I was going to prove — which I didn t, although I think it was true — that the cramps of swimming came from alkalosis, a result of overventilation. The overventilation showed up very nicely the moment my buttocks touched the cold water. Assistants had taken a sample of blood beforehand, and the idea was to take a sample after and show that the pH had gone up. It took them twenty minutes to get the second sample of blood. In the mean time there I was in the water and once in a while the sadistic interns would splash more ice water on me. After twenty minutes they got a few cc of blue-black blood which, of course had a very much lowered pH. So I proved the opposite of what I wanted to. I think if we had had arterial punctures in those days I would have been on the right track.

Talbott This Conference is concerned primarily with the fundamental aspects of cold. In discussing with Dr Fremont Smith the subjects for consideration, it was obvious that if we keyed our remarks to the applied level we probably would neglect several of the fundamental aspects. The subjects assigned, therefore, which are to be of short duration with the discussions occupying a major portion of our time have no direct clinical bearing.

The five subjects for discussion will in no way cover the field of cold injury and the introductory remarks in each instance are to be precisely that — introductory rather than definitive.

The purpose of this Conference in keeping with the policy of all Macy conferences, is informal discussion with each one participating whenever the spirit moves. Are there any comments regarding the general purpose of this Conference?

Fremont Smith Let me say one word about the discussion. Dr Talbott is quite right when he says that we focus our attention on the fundamental biological physiological climatological, and geographic problems, but that doesn t mean that the discussion need be inhibited in any way. It may range in any direction. It has been our impression our experience in fact that you can always move from discussion of

fundamental problems to practical and realistic problems without difficulty but if you focus your attention on the clinical aspects of a situation it is more difficult to move back to the fundamental plane. We think of this as a program in which we hope to do something to advance fundamental knowledge on problems of cold during a five year period.

There are many practical problems that the Armed Forces have to meet tomorrow and the next day Some of those will come up in discussion, and you should feel perfectly free to let the discussion range as widely as you wish. But when the next topic comes up we shall revert to fundamentals again, at least in the beginning in the presentation hoping that in that way through a five year period, we shall make a contribution to better communication at the fundamental level.

Talbott From now until five o clock this afternoon we are going to consider animal studies If anyone does not have an opportunity to have his say this morning on the subject, there will be time this afternoon to correct the deficiency Are there any questions?

Burton Is this morning s subject local hypothermia?

Talbott You will note from the agenda that tomorrow we will consider generalized cooling, hypothermia, and acclimatization This evening we have scheduled homeostasis It is obvious that one cannot segregate subjects completely and it is inevitable that aspects of cold injury not scheduled may be brought into the discussion from time to time.

Fremont Smith We cannot segregate subjects completely and we do not want to The point is to be inconsistent. The logical aspects of science are the ones we all hear about, and to which emphasis is given but in the laboratory many things happen which we keep dark. Here we want a chance for the illogical, the creative, the hunch aspects to appear We want a really free association, so that if somebody says something which evokes a question, an inquiry a hunch, or an idea, that is the time to speak of it. We want to have as uninhibited a group as possible.

ANIMAL STUDIES

HARRIS B SHUMACKER JR.
Department f Surgery
U niversity f Indiana Med al Center

I SHOULD LIKE to start the discussion by attempting to answer the question whether animal experimentation is applicable to the problem of regional cold injuries in man. First, I should like to review very briefly some of the fundamental features of the problem as it relates to man in order to see whether there is valid reason for hoping that animal experiments may contribute useful information.

As you well know there are a variety of regional cold injuries (1–15) fundamentally similar but differing somewhat in respect to the condi tions under which they occur the apidity of their development, the severity of the injury sustained and the characteristic features f their sequelae First there is the large group in which the njury is sustained from exposure to more or less dry cold These are further d vided into true frostbite, in which actual freezing of the tissues to ice occurs and milder injuries in which the tissues are not actually frozen. Frostbite may develop gradually over a period of hours or days o less commonly it may develop with remarkable rapidity The latter occurs when there is exposure to exceedingly low temperatures, particularly in the presence of strong winds, and when there is d rect contact between the exposed part and some cooled object It may occur on the ground but more often has resulted from accidents during high-altitude flying

In another group of injuries wetness is a fundamental causative factor Of course, wetness of the exposed part will also increase the susceptibility to injury in frostbite because of the capacity of water to facilitate the transfer of cold to and heat away from the body I the development f immersion foot and trench foot, however wetness is seemingly almost a important as cold itself Such injuries are ord narily sustained over period of days or weeks in ambient temperatures which are generally slightly above freezing The tissues do not freeze, but the resultant damage may be very severe

In this brief outline I have mentioned only a few points, and f r the sake cf brevity I ha e omitted reference to other factors of importance such as constricting clothing, immobility lack of muscular exercise vascular status, and so forth. Nevertheless, the outline will serve to emphasize certain d fferences in the mode of production of the arious cold injuries Now let us examine the result of such injuries.

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Department of Surgery, University of Indiana Medical Center

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As you well know there are a variety of regional cold injuries (1–15) fundamentally similar but differing somewhat in respect to the conditions under which they occur, the rapidity of their development, the severity of the injury sustained, and the characteristic features of their sequelae. First, there is the large group in which the injury is sustained from exposure to more or less dry cold. These are further divided into true frostbite, in which actual freezing of the tissues occurs, and milder injuries in which the tissues are not actually frozen. Frostbite may develop gradually over a period of hours or days or, less commonly, it may develop with remarkable rapidity. The latter occurs when there is exposure to exceedingly low temperatures, particularly in the presence of strong winds, and when there is direct contact between the exposed part and some cooled object. It may occur on the ground but more often has resulted from accidents during high-altitude flying.

In another group of injuries wetness is a fundamental causative factor. Of course, wetness of the exposed part will also increase the susceptibility to injury in frostbite because of the capacity of water to facilitate the transfer of cold to and heat away from the body. In the development of immersion foot and trench foot, however, wetness is seemingly almost as important as cold itself. Such injuries are ordinarily sustained over a period of days or weeks in ambient temperatures which are generally slightly above freezing. The tissues do not freeze, but the resultant damage may be very severe.

In this brief outline I have mentioned only a few points and for the sake of brevity I have omitted reference to other factors of importance such as constricting clothing, immobility, lack of muscular exercise, vascular stasis, and so forth. Nevertheless, the outline will serve to emphasize certain differences in the mode of production of the various cold injuries. Now let us examine the result of such injuries.

One potential consequence is gangrene, or necrosis of tissue. Extensive gangrene necessitating loss of significant portions of the injured area constitutes indeed, the most dreaded sequel which may develop In true frostbite the development of gangrene and its extent appear to be correlated with the duration and severity of the exposure and the extent of the part exposed. Yet freezing is not essential for the production of tissue necrosis Gangrene of variable extent occurs all too frequently in trench foot and immersion foot, and it may occur in the milder injuries resulting from exposure to dry cold, though in such instances it tends to be limited and superficial Whenever vesiculation of skin or necrosis of tissue is present the possibility of infection exists. This matter of infection, once very grave, has become much less a threat now that the importance of good local care of the injured area is understood and now that effective antibiotics and chemotherapeutic agents are available The problem of gangrene and its prevention is certainly one we shall have to keep in mind during this discussion.

Another problem concerns injuries to somatic nerves. Temporary paralysis of important nerves is occasionally a real problem in immersion foot. After such an injury the individual may have, for example, a perineal paralysis with typical foot-drop gait. There may be present in trench foot, and to a lesser extent in frostbite, evidence of minor neurogenic damage such as small areas of hyperesthesia, hypesthesia, or even anesthesia, but motor paralysis is usually conspicuous by its absence in these conditions Furthermore, some of these alterations in nerve function are apparently not due to organic injury to nerves but to impaired circulation, and can be eliminated by sympathetic denervation The likelihood of extensive somatic nerve damage, then, seems to be greatest in immersion foot and least in frostbite, with trench foot occupying an intermediate position.

Another related problem concerns painful sequelae Some of them are apparently associated with altered vasomotor function or sympathetic activity since they can be eliminated by sympathetic interruption. Some, however are seemingly unrelated to circulatory changes, and are not influenced by sympathetic activity or paralysis. There is good histologic evidence to suggest that the latter may be dependent upon scarring about small nerves and nerve endings (16) These painful sequelae are a very real problem in trench foot and immersion foot They constitute a relatively minor problem in frostbite, whether it be ground frostbite or high-altitude frostbite, most of the serio[illegible]s in this condition being relievable by sympathectomy

Finally there is the comm[illegible] in vaso-motor and sudomotor function. I[illegible] may initially be presen[illegible] su[illegible] athetic

activity but after a time there is apt to occur sympathetic overactivity with a tendency to vasoconstriction, hyperhidrosis and cold sensitivity In some individuals these changes are slight, in others very serious In some they appear to be transient, while in others they are persistent or even progressive Fortunately if they are severe and persistent, they can be treated with rather general success by sympathectomy

As we review these sequelae, we are impressed with the fact that the various types of cold injury have in common the possibility of tissue necrosis and the likelihood of development of altered vasomotor and sudomotor activity Fortunately gangrene develops in a small percentage of cases only and in most of them the necrosis of tissue is not extensive Fortunately too though changes in vasomotor and sudomotor activity are common, these alterations are often not serious, and if they are serious are amenable to treatment. Damage to somatic nerves and painful sequelae resulting from scarring about nerves and nerve endings appear to occur much more often in injuries attributable to wetness and coldness than in those resulting presumably from exposure to more or less dry freezing temperatures

Unfortunately there have been only a few attempts (17 18) to produce experimentally the immersion-foot and trench-foot syndrome Though these efforts were successful in reduplicating some of the essential features of these conditions, gangrene did not develop except ra ely when there had been superimposed pressure or local infection By and large, the chief contributions from animal experimentation have concerned only true frostbite. In order to put them, important as they are, in their correct perspective it must be pointed out that true f ostbite, with actual f eezing of tissues to ice, occurs far less commonly in man than trench foot and immersion foot and the milder nonfreezing injuries resulting from exposure to dry cold.

Since the most satisfactory methods of producing standard, controllable, and reproducible frostbite lesions in experimental animals have involved rather rapid f eezing of the exposed tissues, generally by immersion in a freezing mixture, it is important to consider the suitability of such injuries for study Fortunately in the case f human frostbites, we have examples of rapidly induced freezing injuries to compare with those which develop more slowly I find no essential difference between these conditions Frostbite that has developed very rapidly for example, in cases of high-altitude frostbite is quite similar to the commoner frostbite injuries that re sustained during a longer exposure on the ground. The acutely injured tissues appear essentially the same and the sequelae are essentially the same This similarity is very important Unless this assumption is correct, and there is no fundamental difference between human frostbite of slow or very apid development, then the results of study

of rapidly induced experimental frostbite in animals may have very limited applicability to the problem of frostbite in man. If on the other hand, this impression is correct, the animal experiments would seem, in all likelihood, to have real validity

Further evidence of their applicability to the problem in man comes from the similarity of the lesions produced. The experimental lesion is quite similar to that seen in man, and all grades of injury may be produced in animals Indeed, in the case of the more severe injuries in animals as in man, all degrees of injury are present in the same extremity varying from the mildest changes in proximal portions to gangrene in the more distal parts Further belief in the validity of animal experiments would seem justified from the facts that experimentally produced frost bite appears to be quite similar in a wide variety of species, and that it generally responds in like manner to similar measures in all of them.

It is most important that Colonel Blair and his associates (19) at Fort Knox have recently produced frostbite in experimental animals by relatively long periods of exposure to low ambient temperatures rather than by immersion of an extremity I hope he will speak about this work. It is a very fundamental contribution. Now that it is possible to produce frost bite experimentally in a manner more similar to the method of development of the common variety of frostbite in man, it should be possible to find out quickly whether or not this type of frostbite is similar to that previously used in animal studies in its basic physiopathology and in its response to treatment. For the moment the considerations just enumerated suggest that these new studies will probably confirm those already performed.

Assuming that the animal experiments are valid, to what phases of the frostbite problem are they applicable? First, let us consider the problem of gangrene. It is precisely with regard to gangrene that animal experimentation has made its chief contribution to therapy Indeed, the incidence and extent of necrosis have thus far proved the only reliable yardstick by which to measure the effectiveness of therapy

It is not my purpose now to review the results of these studies, but it may be appropriate at this time to point out that these animal experiments are in complete agreement only upon one point They all indicate that the immediate momentary application of moderate warmth to the still frozen part in order to bring about its rapid thawing constitutes by far the most effective therapy which can be applied (20– 6) They have demonstrated some apparent salvage of tissue from the administration of rutin (25 27) and also from the use of antihistamines (25 28) They have given variable results as regards the effectiveness of sympathetic interruption and general vasodilating agents (23 24 27 29 30 31) some experiments showing no benefit some moderate benefit. They have been

completely contradictory with regard to anticoagulant therapy (23 24 27 32–38) some having resulted in no improvement whatsoever some in moderate benefit, and others in amazingly good protection from tissue necrosis

The neurogenic damage to which I referred is reproducible in experimental animals. Severe experimental freezing injuries may be followed by definite nerve paralysis Yet animal experimentation has up to the present contributed little to this problem. Animal studies have resulted in no contributions to the problem of the painful sequelae which may follow the cold injuries in man. Thus far there have been no significant contributions from animal studies to the problem of the vasomotor sequelae which so commonly follow human cold injuries. I am not very hopeful that animal experimentation will prove very fruitful in these directions. It is primarily with the prevention of tissue necrosis and the understanding of the basic physiopathology of frostbite that such experiments seem to offer the greatest promise

I do not think that animal experimentation should be restricted in any sense Any idea which may contribute to a better fundamental understanding of the cold injuries should be pursued. In order not to lead ourselves far astray when it comes to the question of treatment, I think we should always keep in mind precisely what the clinical problems are

Let us consider one of the therapeutic measures that currently is being studied in a variety of conditions namely the use of the adrenocorticotropic hormone and cortisone. These agents have been used in frostbite also and, though no experiences are yet published, it is my understanding that no clear-cut benefit has resulted Animal studies provide no evidence that the adrenocorticotropic hormone modifies the outcome whatsoever so far as loss of tissue is concerned (26) The question then naturally arises whether these drugs might be potentially useful in inhibiting scarring. As experimental evidence accumulates it becomes increasingly apparent that the inhibition of fibrosis in general is not constant under treatment with the adrenocorticotropic hormone or cortisone and that effects are apt to be noted only when massive doses are used. Under any circumstances we must ask ourselves the question whether scarring and fibrosis is a real problem in human frostbite a large enough problem to warrant use of potentially dangerous drugs.

Actually except for the minute scarring about small nerves and nerve endings that is apparently responsible for some of the painful sequelae, especially in trench foot and immersion foot, fibrosis and scarring constitute a relatively small problem in the cold injuries Ulcerated areas heal without significant induration and scarring, and the end result is much the same as with the healing of ulcers situated in the same areas and requiring the same time for healing in other conditions As in other conditions,

they heal with minimal scarring when they heal promptly and without infection. If large, their healing should be facilitated by the use of skin grafts rather than by allowing them to epithelize slowly from the edges. Actually by and large, the healed extremities of patients with cold injuries have good, healthy and relatively pliable skin. On rare occasions an unexplained tendinous contracture of a real periarticular fibrosis may develop Generally however contractures result from unbalanced muscle pull upon digital stumps after partial amputation or in cases in which the individual keeps a digit immobile without muscular exercise for long periods Under such conditions one would not expect any drug to be effective More often than not, apparent decrease in mobility is due to long disuse and weakness of muscular effectors rather than to real periarticular fibrosis In a few persons with residual Raynaud's syndrome, sclerodactylia may develop as a late sequel, and in a few whose cold injury has resulted in obliterative arterial changes trophic alterations in the skin may develop years afterwards. Altogether one would conclude, however, that the problem of scarring and fibrosis is a relatively small one in human frostbite.

It seems fairly clear from animal experiments that the resultant damage from frostbite can be modified provided proper treatment is administered immediately This is evident from experiments with rapid thawing in which the treated group may survive with little or no apparent damage, while in the untreated control group extensive gangrene develops. Other experiments suggest that certain additional measures may be moderately effective. Thus far all of these studies would indicate that the presence or absence or degree of tissue necrosis which follows frostbite depends primarily upon the severity of the freezing injury and the treatment which *is instituted as an immediate emergency measure*. Evidence of the effectiveness of therapeutic measures applied later after thawing has taken place is less convincing It would seem wise to keep in mind the distinction between the emergency treatment of frostbite and its subsequent treatment.

I have spoken of the fact that alteration in the vasomotor status of the injured extremity is the commonest sequel after regional cold injury It is too bad that animal studies have thus far not been productive along this line One of the fundamental defects of such studies is our comparative lack of knowledge of the normal peripheral vasomotor behavior of experimental animals and of their response to sympathetic blockade. We know a great deal about the circulatory behavior of normally innervated and sympathetically denervated human extremities in ordinary environmental circumstances and upon exposure to moderately cool and warm atmospheres Similar information about the commonly used laboratory animals is lacking Studies which my associates and I have initiated in

order to obtain such information have unfortunately not progressed sufficiently far to permit conclusions to be drawn from them. These exploratory observations would seem to indicate, however that there are important differences between some of the laboratory animals and man. Some of the laboratory animals appear to have much more stable circulation of the extremities under ordinary circumstances and upon exposure to a moderately cool atmosphere there appears to be much less apparent difference in the circulation of normally innervated and sympathetically denervated limbs than is true in man. I believe we shall have to study the vasomotor responses of the various laboratory animals as carefully as we have explored this field in man. I believe our interest in the cold injuries is going to force us to broaden our knowledge about the peripheral circulation of laboratory animals.

Horvath Therefore, you would suggest that perhaps the use of some blocking agents might be a nice tool to help evaluate this. I am thinking in terms of a recent report that tetraethylammonium chloride was not of value in preventing the aftereffects of frostbite whether it was given prior to or immediately after the rabbit (I think it was a rabbit) was frozen.

Shumacker Yes, Dr Horvath, I think that a great deal more work of this sort must be carried out particularly since the results with sympathetic blockade and the use of general vasodilating agents have given such conflicting results in experimental frostbite It is true that one group of workers has recently reported failure of tetraethylammonium chloride to reduce the incidence or extent of gangrene in frostbitten rabbits. There have been several other studies in which similar measures have apparently been of benefit. Such studies should be continued until the matter is better clarified.

Kark Your discussion deals mainly with serious injury as a result of cold. There are at least three other conditions in man which I think need discussion in relation to animal experimentation cold allergy chilblains and the Raynaud's syndrome (39) Do you think that one can do studies on animals in relation to these three conditions, or do you think it is better to do investigations on man?

Shumacker I think that the only observations which have proved valuable are those which have been made on man. Lempke and I tried to find out whether the dog's foot tended to be cold-sensitive after frostbite, but we obtained no conclusive data (40) I feel that we should continue to explore the possibilities in animals, but I have the distinct feeling that we shall have to rely pretty largely upon studies in man to advance our understanding of such things as chilblains, cold allergy and Raynaud's phenomena following frostbite.

Fremont Smith Have there been good studies during life, that is, watching the circulation under the microscope during chilling, and have

there been good histological studies of material sectioned at various stages of chilling? If so I wish you would tell us what actually happens, for instance to an animal's skin and subcutaneous tissues when they are chilled What goes on that could be seen if you were observing the circulation in the rabbit window — if that has been done — and what goes on if you look at it under the microscope? Does it take five minutes, ten minutes twenty five minutes and so forth?

Talbott You are talking about changes not associated with severe damage

Fremont Smith I am speaking of all degrees of change down to freezing I should like to know what you mean when you say freezing

Edholm May I interrupt concerning the word freezing ? There are some difficulties in its use, in that we keep on thinking of freezing as occurring at 0 C. That presumably is not the freezing point for living tissue, and I should very much like to know particularly in human tissue, at what temperature we get actual freezing By freezing I take it one would mean the appearance of crystals in tissue At what stage does that occur? Is it a necessary phenomenon for the production of frostbite, or is it something that is so far down the temperature scale, so far as environmental conditions are concerned that it doesn t occur often?

Horvath Tissues are supposed to freeze at −25 C. instead of around 0 C

Gottschalk Centigrade?

Lewis I do not know about human beings. I can tell you exactly where animal tissue freezes at −2 2 C. This does not take into account the phenomenon of supercooling (which occurs sometimes) as described by Sir Thomas Lewis (41) He froze down to −19 C. in some human beings without freezing the skin. You get that in muscle, too We had a Brown potentiometer record down to about −5 C. or −6 C., and it jumped back to −0 5 C. I wrote to the company "What is the matter with your instrument? I had a man come over from Houston to fix the instrument, then I said I cannot have this going on so I got another one, put a thermocouple on that and put it through the same hole in the leg and it also jumped So I knew it was a physiological phenomenon.

If you do not have supercooling, animal tissue freezes at −2.2

Horvath What do you mean by freezing ?

Fremont Smith Yes, what do you mean by freezing ?

Horvath Blood is −2 and muscle tissue is supposed to freeze at −5

Lewis Muscle freezes at about −2 2 C.

Kark I should like to have a definition of frozen tissue

Lewis Just as this tissue here is frozen tissue

Kark Histologically

Burton You have to define it in terms of physics, in terms of ice crystals. Freezing means change of state from the liquid to the solid

Fremont Smith As you defined it a minute ago freezing is when it feels hard

Lewis That is right, like ice.

Fremont Smith I think that raises a very interesting point, because, you see, our argument could go back and forth. What we mean by freezing with respect to feeling hard may be quite different, histologically from freezing with respect to being crystals, identifiable crystals of water in a solvent or solution

Barton And the test of that is this jump of the temperature which is proof that that has happened.

Crismon I have a slide that will illustrate that for rabbit tissue

Lewis I have a graph here of the temperature curves in the rabbit's leg during exposure to a cold alcohol bath (Figure 1) The thermocouple

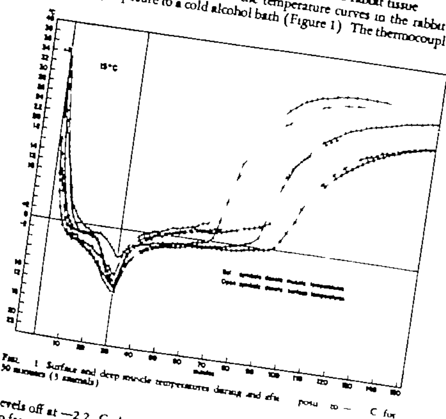


FIG. 1 Surface and deep muscle temperatures during and after exposure to — C for 30 minutes (3 animals)

levels off at —2 2 C At thawing it does the same thing. It takes energy to freeze and to thaw it It levels off

S M Do you refer to the latent heat of crystallization

Lewis Yes.

Siple You speak of a jump Was that an actual jump in the thermocouple reading?

Lewis That is right

Siple That ties in with the phenomenon of feeling that we call the ping When a person has had his cheek frozen a number of times, he learns to recognize a minute but very sudden, sharp pain simultaneous with the instant that the cheek begins to turn white and freeze.

Lewis Of course that only happens once in a while. Perhaps out of twenty animals you will get two or three that jump The others go on down, and stay below freezing Going across the freeze-temperature rapidly we got the jumps back to −0 5° C.

Fremont Smith It happens only occasionally

Lewis Why the temperature jumps back to −0 5 C instead of −2.2 C I do not know since the latter is the freezing point of tissue.

Fremont Smith So it is not a characteristic phenomenon.

Lewis No

Burton The supercooling depends upon having very few nuclei on which the crystals start. Then if you have a crystallization, you will get this recalorescence, this heat jump If you do not have supercooling, then you get this flatness of the curve, which is the key to the thing

Fremont Smith If I understand it, you then —

Burton The flattening happens at the point at which the change of state is happening The external cooling is taking heat from water to form ice instead of lowering the temperature

Fremont Smith It is not the supercooling If I understand correctly now it is what happens after supercooling, when you get a sudden precipitation of crystals. In the sudden crystallization after supercooling you get this upriusing Is that right? It occurs when the calories are released.

Burton If you do not have any supercooling, if the moment the tissues reach the freezing point, crystallization begins without the temperature going below it then you won t have this jump you will just have the curve of cooling and a flattening off until all is frozen

Horvath What is the factor that determines whether you have super cooling?

Burton All sorts of things, mainly absence of nuclei — even sound will start it, or seeding from another area by a crystal

Horvath Insertion of a thermocouple needle will do the same thing

Burton Yes

Minard I should like to follow up what Colonel Lewis has said by commenting on the findings of Lewis and Love (42) These investigators occasionally observed the phenomenon of supercooling in human skin to which a chilled copper bar was applied. Supercooling could not always be induced, and occurred only under special conditions. As I recall,

the skin must be extremely clean, and oily skin was more likely to exhibit the phenomenon than dry skin.

Burch Isn't it also true, in a more recent paper that Lewis (43) was able to produce supercooling in every instance if he was so inclined. The trick is to keep his copper bar completely dry If crystals of water are permitted to form on the bar the crystals liquefy on contact with the skin and permit rapid transfer of heat and better cooling. If he kept the copper bar completely dry supercooling occurred almost invariably Lewis was able to cool down to −20 C. and −22 C. without freezing the skin.

Talbott Dr Crismon, do you have any comments on your slide?

Crismon I simply wanted to furnish this as evidence (Figure 2) (44)

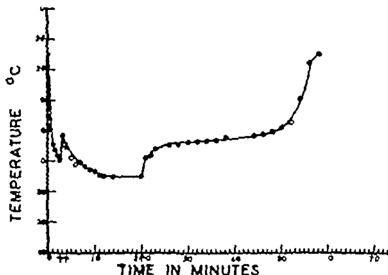


FIGURE 2 Deep-tissue temperature in rabbit foot during freezing (20 minutes at −15 C) and thawing. Reprinted by permission from Fuhrman, F A and Crismon, J M *J Clin Investigation* 26, 239 (1947)

It may be a little easier to see than Dr Lewis chart A thermocouple was placed deep in a rabbit's foot immersed in a cooling mixture at −15 C. The temperature change shows the recalorescence described by Dr Burton followed by a further decline in temperature after the crystals had formed When the foot was removed from the cooling mixture after twenty minutes, the rewarming curve shows a long plateau without evidence of re-entry of blood until some forty or fifty minutes had passed.

Talbott And this was reproducible in a high percentage of animals?

Crismon I do not know how many times this went on. We measured it in a very few of them only When we used this temperature of exposure, it was a very common experience I do not think we had any exposures at this temperature with the thermocouple in place where we could not see it. Of course, the placing of the thermocouple is a traumatizing procedure and may have contributed to the changes illustrated. When we used lower temperatures, such as −55 C., no such recalorescence was noted. The feet were frozen. The temperature curve was smooth when the foot was removed from the freezing mixture and thawing occurred The latter part of the curve has the same general characteristics as the one from the twenty-minute period

Fremont Smith Do I understand the physics of this correctly? Is this the same kind of phenomenon as that of supersaturation, where if you drop your crystals into a supersaturated solution you suddenly get a full crystallization, either with the absorption of heat or with the release of heat, depending upon the substance? Is this a sudden crystallization of ice from a supersaturated solution in which, as the ice forms it releases heat, and hence causes recalorization?

Burton That is right There is a rich source of study of this phenomenon in the work of the entomologists Insects show this You can take them down to perhaps 25 below zero and they do not die therefore they have a very intense supercooling Then all you have to do is just touch the skin with a little crystal ice, and they are dead

Fremont Smith Then they freeze

Burton If you put a thermocouple in them, the temperature will go down to 20 below the moment the freezing happens, the temperature shoots up almost to zero This supercooling can happen in insects, and does happen very frequently and the insect goes on flying around, and so on, at 20 below

Fremont Smith He continues to fly

Burton That is one way of killing a mosquito in the Arctic catch up with him and touch him with a little bit of ice, and he is dead

Burch An interesting note appeared four or five years ago It described the process of bringing a drop of water down to −70 without freezing, by lowering it into an atmosphere on a very carefully cleaned glass spatula. Then by sudden agitation the water crystallized That could be reproduced with proper preparations

Sellers According to the author he was able to control the conditions, so that freezing could take place at practically any chosen temperature down to the minimum mentioned by Dr Burch

Fremont Smith Is there general agreement about the temperature at which the skin will stabilize once freezing does take place in terms of ice crystals being formed, the temperature that you mentioned, sir?

Lewis I would just like to ask Dr Crismon a question. Does your temperature level off at −0 5 ?

Crismon I do not remember where the level point was.

Lewis Ours leveled off at −2 but a very interesting thing confused us As I said before when the temperature in the rabbit legs jumped from −5 or −6 C it went to −0 50 C instead of to −2.2 C

Crismon The level looks a little bit lower to me on this graph. The −5 would be closer to 0

Lewis Oh, that is −10 As I say our graphs here leveled off at about 2.2, which is what Sir Thomas Lewis gives

Crismon The midpoint of the plateau lies at about −2 5 C

Talbott That is the warming-up period

Fremont Smith It is the height you get to on warming up that is a power of phenomenon isn t it?

Barton The heat you e using to warm it up does not raise the temperature so long as it is all used to melt the ice so the temperature stays level.

Fremont Smith So that the point of ice melting would be the same temperature as that of ice freezing

Barton Yes.

Burch How long was the part in the f eezing mixtu e

Crismon The graph begins at 0 time It would be bout 2½ minutes to ice formation. Following the heat of freezing there was a further decline The total period of exposure was twenty minutes but I should say at least some ice formation occurred in three to five minutes

Horvath It would ppear therefo e that the freezing occurred somewhere below 0 and the 0 is not representative of the f eezing phenomenon.

Crismon The point we measured was not epresentative of the entire foot, I am afraid It is frequently forgotten, in thermocouple use that the instrument measures point temperatu e

Burch Was the thermocouple deep n the tissues? How did you know when the deep tissues were frozen in differentiation to the superficial tissues of the foot

Crismon Ou aim was to measure the temperature in the deep tissue We could tell pretty well the state of the outside.

Burch No but to know it was frozen in the vicinity of you thermocouple, did you use that little ecalorescence-elevation gr ph as n index, the point at which the thermocouple was f ozen, or did you touch the outside?

Fremont Smith What was the evidence of its freezing at the point of the thermocouple?

Crismon This is the best physical evidence we have

Burch That little jump in temperature?

Crismon Yes but we did not rely on that in our experiments. We did not put a thermocouple in every animal that we exposed to cold.

Sellers Are we still concerned with skin only in this graph?

Fremont Smith Tissues more broadly

Sellers Is the discussion we have been having pertinent to this graph at all? It is in a very general way but we have been talking specifically about the freezing point of skin.

Talbott Colonel Lewis said by definition that freezing was hardness This is hardness of the skin I presume

Lewis It turned out to be the same for muscle and skin as far as I can tell Sir Thomas Lewis says it is −2.2 C. That is what we decided muscle was so I don t think there is much difference

I should like to ask Dr Crismon what thermocouple wire he used We used 30-gauge wire.

Crismon This is 27 gauge.

Horvath We have seen this with 36-gauge, and with 42 The same thing occurs regardless of the size.

Kark What cools the depth of the cell? Is it crystal formation, or the length of time, or is it supercooling?

Barton Is there anyone who can report on the work that is going on at Bethesda? I remember that at the International Physiological Congress last summer Luyet was reporting experiments with thin films of embryonic heart tissue, how you could quick freeze the tissue in liquid air and have it live afterwards If things are frozen quickly enough, the crystals are so minute, submicroscopic perhaps that you do not rupture the cells and you do not get dead tissue. I know this work is going on at Bethesda.

Dr Behnke, are you familiar with the results so far? What happens in an animal is the question, whether you ever get quick enough freezing to escape the rupture in the skin.

Siple You do in quick freezes of the face with strong winds at low temperatures There is no apparent damage because of a quick freeze. The extent of damage is generally limited to the sloughing of skin, and not always to that.

This is really as Dr Sellers has pointed out, freezing of total tissue as contrasted to freezing of skin Dr Frazier (45 46) medical officer of the U S Antarctic Service in 1940 took stop-watch timings of the length of exposure to wind chill that caused men s faces cheeks, noses or ears to freeze He could clock the instant that freezing occurred by the appearence of sudden blanching which corresponded to the moment the subject flinched at the ping sensation of the onset of freezing Freezing started as a very tiny spot, and then gradually grew in area.

I think the question of supercooling has to be watched rather care-

fully to prevent overemphasis I did a series of about a hundred experiments in freezing a cylinder of water and whenever the wind was perceptible from one direction, even though apparently not enough to shake the instrument, I never observed supercooling The only occasion on which I actually witnessed supercooling was when it was so calm that I could detect no directional wind Cooling was progressing, and the temperature went below the freezing point My observation depended upon the accurate timing of the period that the temperature leveled off at the freezing point during the time the water was giving up its latent heat of crystallization. Puzzled by the absence of a leveling off" of the temperature on this occasion, I went out to examine the cylinder It was still all water until I touched the cylinder Then suddenly the water turned mostly to ice, and the temperature shot back up to 32 F

Horvath I want to emphasize what Dr Burton said earlier namely that any modification of stimuli or any modification of factors at all on the skin or in the tissues themselves would be sufficient to set into action the supercooling

Burton Such as vibration, sound, percussion.

Edholm When we get to a white appearance in the skin which we term a frostbite, have we then got crystal formation in the tissues or even in the cells of the skin?

Siple Certainly as far as faces are concerned

Fremont-Smith I think we ha e reached a crucial question. How can we relate the observance by the eye and the feel on the surface with what goes on in the tissues, by temperature measurement, for which there is some data, and also microscopically? Is there any way of telling microscopically whether there have been crystals formed or not? I am under the impression, from the discussion so far that there isn t good correla tion between what goes on within the tissues and what we observed on the surface. There is a good deal of inference Now have we got any clear clean data that show us what happens?

Horvath In the destruction of the tissues, there is certain to be ice formation

Fremont Smith What is the evidence of that?

Burton I would put it the other way If there has been ice formation, unless it is the peculiar kind of ice formation that you get in very rapid freezing, then there is certain to be tissue damage

Fremont Smith Now we have two assertions

Burton If you do not see tissue damage, I would say there cannot be ice formation unless it is this peculiar ice of quick freezing

Siple I do not think this quick freezing is as peculiar as you seem to think.

Sellers I agree with Dr Siple. I have spent a large part of my life in the

Midwest, and there in very cold weather it is quite common to get small areas of the cheeks or ears frozen. Some physiological changes occur because the skin isn t quite the same afterwards, but it certainly doesn t slough off it isn t dead

Fremont Smith Gentlemen we have two assertions here which are contradictory but in neither case is any evidence given. One assertion was that if there is tissue destruction, there is ice formation, and the other assertion was that if there is ice formation, there is tissue damage. Neither of you gentlemen gave any evidence any data, to show that your conclusions would be justified I am not saying there is not any data. What is the data that relates crystal formation to tissue injury?

Siple If we can assume hardness, we would have it.

Talbott Does hardness mean damage?

Siple No it means ice

Talbott Does not ice mean damage?

Siple Not necessarily if caused by quick freezing.

Burton Dr Cole, with Dr Meryman, is working on this, and he has an extremely sensitive measure of tissue injury He measures the presence or absence of the physiological membrane in muscles by the impedance of muscle If that has been changed, then there has been damage to that membrane this is a very sensitive test

Fremont Smith Can you relate that to crystals?

Minard I might attempt to answer the questions of Dr Burton and Dr Fremont Smith about the work being done at Bethesda I am sorry I cannot give a complete or detailed account of it However Dr Meryman has been interested in studying the freezing process under simple conditions such as the freezing of a thin film of water He has used the electron microscope and more recently the X ray diffraction apparatus to examine the frozen film. He has also examined frozen specimens of solutions of crystalloids and colloids One of the important findings is that rapid freezing results in extremely small crystal formation.

Burch May I ask you what rapid means?

Minard Of the order of milliseconds

Burch You say small crystals You mean from the point of view of the crystallography?

Minard From the point of view of the appearance in the electron microscope. In other words Dr Meryman at times obtains a picture in the electron microscope which shows essentially no structure This would suggest that the crystals were approaching molecular magnitudes.

Burch Do you mean the difference between the size of an ice cube and a big block of ice when you say crystal size? Aren t the crystals that form these two the same? Or are they different? That is, if you had a block of ice and an ice cube, would the crystals be different?

Minard There would be no difference in the structure of the crystal, as might be determined by X ray diffraction but the over-all size of the crystal can vary from microscopic to submicroscopic. However I am completely out of my field.

Birch My impression is that a molecule of water consists of several H_2O complexes arranged in the form of hexagons. When you speak of a crystal, a point not made clear by Dr Meryman in the conference in Washington, are you speaking of sizes of pieces of ice — for example the size of an ice cube and a large block of ice? My impression is that a crystal of water is the same regardless of the size of the block of ice.

Siple I think you can bring it down to this. When we speak of the small crystal we are speaking of a crystal small enough to be contained within an individual cell without bursting through its wall, and independent from other crystals forming in other cells.* We have learned quite a bit about quick freezing of tissue from the frozen food industry which has discovered that production of small crystals by quick freezing does not break down the tissue, and thus upon thawing yields a natural-looking product. When the food products are slow frozen, big ice crystals are formed, and when the food is thawed it becomes mushy

Barton It is simply mechanical and in relation to the size of the cell. If you take a silk stocking and put a lot of big ice cubes in it, you break it but if you throw little ones in it may not break

Behnke About fifteen months ago we thought that the reason Dr Crismon might have had better results from rapid rewarming was due to the fact that the tissues were cooled rapidly and went through the phase of crystal formation so rapidly that cells were not ruptured by the formation of large crystals, as Dr Siple implied The rapid rewarming, conversely eliminated the probability of crystallization to the point of cell rupture

Siple That follows my observation of face-freezing cases mentioned earlier No damage occurred when the frozen areas were discovered early and promptly and properly rewarmed I do recall at least two or three cases, however in which a frozen face was not discovered by the individual, and therefore not properly taken care of The frozen spots were allowed to thaw at their leisure later on. These cases did incur damage — damage to the extent of heavy blistering and major sloughing of skin.

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* In my opinion, as expressed later in the Conference that the small crystals caused by quick freezing may be even more minute than indicated here, that is, they may be thought of as slightly larger than molecules that freeze in place in the colloid of the cell without creating fractional separation, which takes place when freezing is accomplished slowly Bursting of cell [illegible] is not necessarily [illegible] criterion it is more apt to be destruction of the colloidal state If the colloid is not fractionated, [illegible] is viable upon thawing, but not if it is coagulated or agglomerated.

Behnke To get back to the plants, I am somewhat familiar with citrus horticulture, having had many winter evenings spoiled by the need to go out and do smudging The temperatures in southern California do not get very much lower than 28 F Freezing occurs, and is accompanied by cell rupture which is thought to be augmented during rewarming from sun radiation. The cellular rupture that occurs is easily recognized because the frozen area is dehydrated. So with reference at least to oranges, we associate the injury to the plant cell with the rupture of the cell membrane because of ice-crystal formation and expansion

Fremont Smith You raised an interesting question, Captain Behnke, at the physical level I received the implication that if you supercooled, with very minute crystals forming — not large aggregates — and that if you then rewarm gradually during the process of rewarming, presumably on this plateau level from a supercooled area, larger crystals would be formed that would then destroy Is that correct? If this is true, it seems to me that the fact that rapid cooling and rapid warming are equivalent is crucially important.

It never occurred to me before that during a slow warming larger crystals would be formed when you reached this plateau but if that is true, then you would get aggregates large enough to rupture cells, a process that did not take place when the tissue was first frozen

Burch Isn t it also true that if you keep a part frozen, the crystals (size of the aggregates) will grow even though you rapidly cool with time?

Menard I believe that is correct since molecular movement does not cease entirely until absolute zero is attained As long as there is still some molecular movement there can be reorganization and changes between the phases even though these changes may occur slowly

Sellers Dr Bigelow with this point in mind, has been using diathermy (radio frequency) for rewarming (47) He tells me that his results are encouraging He is able to rewarm by this method as rapidly as by immersion in water at 40 C and with no ill effects.

Talbott That is because you have a depth of tissue to penetrate with heat If one warms superficially one proceeds through essentially the same stages as in slow rewarming irrespective of how rapid it appears to be superficially

Crismon That may explain the difference, too between the successful treatment of a thin structure, like a rabbit s ear and the relatively poorer results that you get with the foot.

Talbott Yes.

Conn Up until this moment I have gotten the impression that everyone has thought in terms of a sac filled with fluid, and that the fluid might or might not rupture the membrane, depending upon the speed with

which it was cooled. Ought we not to keep in mind that the cell membrane itself is made up of a certain proportion of fluid, and that the membrane itself may be more important in its rupture, than what goes on inside the cell?

Fremont-Smith In other words, you are raising the question whether it may not be freezing of the membrane rather than the ice crystals within it, that causes the rupture

Conn Yes.

Crismon May I add one more point from Dr Meryman s work again? During the formation of large crystals, in the rewarming phase, the cells in the thin bits of muscle were observed to become so dehydrated that the crystals grew in the extracellular phase at the expense both of cell water and of extracellular water As the final melting occurred, the cells increased greatly in size by osmotic transfer of water that came from the ice crystal. It was at that point that rupture was observed under the microscope.

Fremont-Smith There were permeability changes in the membrane during this first phase.

Crismon Exactly It would perhaps be more accurate to consider the change as an altered transfer rate of electrolytes

Talbott Dr Shumacker has one sentence he would like to add.

Shumacker Dr Edholm s questions concerning the definition of freezing and the temperature at which freezing of tissues takes place might be extended to include the question whether actual freezing of tissues is necessary in order that real injury be sustained The answer is No As I mentioned before, patients may develop vesicles and superficial gangrene after mild nonfreezing cold injuries, and they may develop gangrene of variable extent after trench foot and immersion-foot injuries in which no tissues are frozen Indeed, it is often difficult to be certain whether actual freezing of tissues has taken place, and because of this difficulty the word frostbite tends to be used rather loosely It is certainly true that it is not possible to obtain evidence suggesting that the tissues have actually been frozen to ice in most of the patients with so-called frostbite In spite of the efforts to obtain a careful history one often is forced to acknowledge that he does not know whether or not freezing took place On the other hand there a e occasions when it is perfectly clear that at least the skin was frozen solid, and other occasions when it is perfectly clear that freezing did not take place True freezing injuries are probably less common than they are generally thought to be

There is an interesting account by Jack Adams-Ray and Carl-Johan Clemedson of cold injuries sustained during freezing weather in 1912 in Stockholm (48) It happens that both Dr Adams-Ray and Dr Clemedson attended the recent National Research Council-sponsored confer

ence on cold injuries in Washington. Their report incidentally contains an excellent résumé of the customs of some of the primitive peoples in respect to the emergency treatment of cold injuries. Their study covers 208 cases. It is interesting that out of the entire 208 only in three was there actual freezing, or as they put it, "congelation with formation of ice.

Talbott These were frostbite studies?

Shumacker These three were certainly cases of true frostbite. Presumably the others were not cases of frostbite in the strict sense of the word.

To return to the original question, I should like to say that, although it is obviously very important that we know in animal experiments whether or not we are dealing with actual freezing of tissues to ice, it is also important that we continue to attempt to study less severe grades of cold injury

Not long ago I saw a demonstration which illustrates with clarity some of the problems that we were discussing a short while ago, and that relate to crystal size and the rapidity of cooling and rewarming. This was a demonstration at Duke University by Dr Keeley Dr Gomez, and Dr Brown. They showed that one can cool a cornea, previously dehydrated in ethylene glycol, so rapidly by immersion in liquid nitrogen that the cornea remains completely transparent. Dr Keeley and his associates apparently feel that this represents conversion to a vitreous state. Subsequently Lieutenant Meryman pointed out to me and to others that one cannot safely use clarity or transparency as an index of vitrification in contradistinction to the frozen state, because perfectly clear frozen liquids, like ice, may be constituted of crystals.

Fremont Smith How long will the cornea stay clear?

Shumacker It will stay clear and transparent as long as it is kept cold and it can be kept clear if it is rewarmed rapidly If you freeze the cornea more slowly it will look opaque and have every appearance of being frozen. If you cool it rapidly so that it remains perfectly clear, but subsequently allow it to warm slowly it will become opaque as it passes from the vitreous to the frozen" state during the process of rewarming To express it with greater accuracy it becomes opaque momentarily as ice crystals increase in size during rewarming and before they disappear

Burch Is it just as hard?

Shumacker These rapidly cooled tissues are apparently just as hard as rock.

Talbott So the feel doesn t determine the presence or absence of crystals.

Shumacker No

Menard Is there any sequela following the rapid thawing?

Shumacker I do not know I do not recall whether they have carried out any studies of the viability of cornea so treated. They have used the dog's skin, however in some very interesting studies that throw light upon this question. They have excised split thickness skin from the dog and preserved it in two ways One part they have dehydrated and cooled with great rapidity in the same fashion as with the corneal experiments. This skin has then been stored at −18 C or lower The other portion of the skin has been frozen by slower methods so that it assumes the usual characteristics of frozen skin This portion also has been preserved in the frozen state. After a while both segments of skin have been reapplied as autogenous grafts to the donor dog Whether they have followed these animals sufficiently long to be absolutely certain of the ultimate outcome I do not know but during the period of follow up the skin which has been subjected to ultrarapid cooling survived normally while that frozen by slower methods did not survive nearly so completely

There are other experiments which also indicate that the more rapidly tissues are cooled and rewarmed, the more likely they are to survive. In studying the final results of transplantation of segments of homologous aorta preserved for a time in the frozen state, Hufnagel (49) concluded that those segments frozen rapidly in liquid nitrogen gave better results than those segments of aorta frozen less rapidly by use of a freezing mixture of carbon dioxide and ether

Barton You have to warm it quickly too?

Shumacker Yes, Hufnagel felt that rapid thawing was just as important as rapid cooling. Concerning the transplantability of homologous tissue and the survival of autogenous tissue after its excision from, and reapplication to, the host, there are data suggesting that the more rapidly tissues are cooled and thawed, the better their chance for survival I am sure that Colonel Lewis and Dr Crismon will agree with me that numerous frostbite experiments have demonstrated that tissues may survive after having been frozen stiff or at least that skin may survive after freezing, and that rapid thawing increases greatly the chance of survival

Barton Don't you think that perhaps we are being fooled by the hardening of the lipids? You may remember Irving's work on the freezing point of the lipids in the reindeer and caribou* and how the melting point changed as you go down the animal's legs, as it would have to Otherwise, how could the fat have got there? It may be that white spots on the cheek aren't any indication of ice crystals at all, but something to do with the fat there becoming hard

Fremont Smith Or a shutdown of the venules

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* Personal communication

Burton This is a domestic problem for every mother in Churchill. They have learned by experience that they have to tell their children that when they are playing outside and their little sister gets one of these spots, they must bring her in right away But they have also learned that there is nothing to be frightened about, that there are no sequelae at all if this is done. On the other hand, if they play there for half an hour with this white spot, then there will be pathological changes.

Shumacker In the Stockholm experience to which I referred a moment ago and in which there were only three cases in which actual freezing had taken place there were 106 in which the exposed part had become white cold, and numb We know of course, from other circulatory disorders not associated with exposure to cold, that whiteness, coldness, and numbness may result from ischemia alone We see these phenomena, for example, in the typical Raynaud s attack.

Talbott Colonel Lewis, did you conduct any studies involving the abdominal wall? This would be of some interest because of the thicker layer of subcutaneous fat than is present on the extremities

Lewis No sir we worked only with the rabbit legs.

Talbott When Dr Burton mentions solidification, does he mean freezing or just solidification?

Burton Solidification.

Talbott The lipids are an important fraction of the subcutaneous tissue One may get a feeling of hardness from solidification following exposure to cold that does not necessarily mean freezing

Burch I should like to ask another question. Could the hardening be due in part to the liberation of small bubbles of gases which become trapped inside and between cells? When the tail or paw of a rat is dipped into cold solution, there is considerable bubbling along the surface of the part.

Lewis I do not know about that

Burch I wonder if trapped air could contribute.

Fremont Smith Isn t that air from the surface roughness of the outside of the rat s tail?

Burch I think in that instance it would be, but I wondered if in these hardened nonfrozen tissues it might not be trapped air —

Fremont Smith Carbon dioxide is more soluble in cold

Behnke Yes

Burch Such as we encounter with the "bends.

Behnke The cooler a solution, the greater the solubility of gases in solution Your thought is that if crystals form, gases are released

Burch Yes.

Burton I think it desirable to dispose of this question of the vitreous state, although it is of very great interest. I myself am convinced, perhaps

on no proper evidence, that this is not something that occurs even in the freezing of a cheek. When we talk about rapid freezing, perhaps some of us do not realize what we mean by rapid. It has to take place in a couple of milliseconds in order to attain the vitreous state — not a couple of seconds but a couple of milliseconds I doubt very much whether physiologically or biologically we ever achieve this vitreous state in the freezing of tissues in the animal It has not been investigated properly but I doubt whether it really has relevance to this discussion

Fremont Smith That is, the very minute crystals?

Barton Yes

Shumacker I think you are right, Dr Burton. I did not introduce the experiments with the vitreous or near-vitreous state as being really elevant to the problem of human frostbite but merely as another expression of the fact that the more rapidly tissues freeze and thaw the smaller the crystals presumably are and the better the chance for survival The studies upon the so-called vitreous state were performed in order to learn more about the preservation of tissues, and not as a potential contribution to the problem of frostbite

Fremont Smith Would you specify now what we have eliminated? The reason is that I don t know how large a crystal can be or how small it has to be for the condition to be called the vitreous state

Burton Apparently there is more involved than just the size of the crystals. There is apparently a new state of water which is not identical with ordinary solid ice I remember that Luyet showed us a beautiful demonstration at the Physiological Congress He dipped a little platinum loop in water then in liquid air and held it in the lantern It was quite clear when it was in the vitreous state As he held it there it warmed up and suddenly a shadow went across it where it had turned into ordinary ice (50)

Fremont Smith But in eliminating that you are not eliminating the concept of minute crystals becoming greater during the physiological warming, are you?

Burton My point is that physiologically I don t conceive that we ever get fast enough cooling of tissues to attain this vitreous state

Fremont Smith But that doesn t eliminate this plateau business and the enlargement of the small crystals we have during rewarming

Burton That is a different matter Supercooling is another subject.

Behnk There is a summary statement in support of what Dr Shumacker and Dr Burton have enumerated from the German experience Most cases of local frostbite, particularly of the lower extremities, are caused not by actual freezing of the tissues but by temperatures near or above the freezing point

Talbott What about Air Force crews exposed to temperatures of 30

or 40 below zero? If a dry finger or a dry hand is placed against metal at this temperature, rapid freezing undoubtedly occurs

Siple I should like to take the other side of this issue, because I think quick freezing of hands and faces happens frequently Just as Dr. Talbott has mentioned it is caused by conductive or contact cooling and severe wind chill cooling, whether at high altitudes or on the ground. I believe that if we examine the sequence of events in thawing we might understand that this phenomenon of clouding of the vitreous state takes place because of refreezing of water particles even while thawing is in progress.

Tissue frozen from the outer surface forms a more or less lens-shaped piece of ice within the skin. It is being warmed by the tissues on the inside that are above freezing as well as by external heat. Liquid or vapor which even recently thawed, if free to migrate to the area of the cold mass of ice, may in part refreeze that is, by exchange of energy during thawing it is plausible to assume that for each couple of molecules that thaw another may refreeze momentarily

Burton You misunderstood me, Dr Siple. I do not mean I think there is no actual freezing of tissue I am sure that occurs. I am saying I do not think there is any analogy to the quick freezing which produces the vitreous state, rather than just crystals, in practice.

Siple I am sorry that I misunderstood you. By vitreous, you mean it will be completely clear ice all the way through.

Burton Yes.

Siple In other words, the limitations that you put on did not include the minute crystals, only the vitreous ice.

Fremont Smith That is the point I was trying to make.

Burton The process of very rapid freezing is used in storing food. I am not aware of the references, but I am sure a good deal of data has been accumulated on how fast the cooling has to be. It has to be very fast just how fast, and whether enzymes are released from cells, and so on, I am sure has been measured.

Shumacker Mr Chairman, I think Dr Burton has made a good point. Data concerning quick freezing to ice would seem to be applicable to the problem of human cold injuries, while data concerning efforts to reach a noncrystalline vitreous state, though of great interest do not appear to be directly related to this problem.

Incidentally as far as I know attempts to reach a so-called vitreous state with biological tissues are doomed to failure unless the tissues are dehydrated before they are cooled in an ultrarapid manner Apparently no matter how rapidly one cools them, tissues tend simply to freeze in the usual fashion, with recognizable crystal formation, as long as they contain their normal water content.

Gottschalk I think we will all agree that crystals are not the only

cause of damage following cold exposure Raker Taylor and others (51) in the Department of Biochemistry Harvard Medical School, report a very pretty study of incubated human red cells in which they used radioactive potassium to measure the rate of exchange of potassium between the red cells and the extracellular fluid These red cells will survive in what is apparently a quite normal state for about forty-eight hours when incubated at 37 C., but when cooled to around 7 C. they immediately begin to leak potassium. Concomitantly with this their rate of glucose utilization goes down. So here is a pronounced biochemical change occurring at a temperature not even approaching the temperature at which crystals form.

Sellers Mr Chairman, one other point that Dr Burton s remarks do not clarify is Dr Edholm s original question, or a modification of it How do you diagnose actual freezing and how important is it to make such a diagnosis?

Almard The question is whether one can diagnose actual freezing —

Talbott At the time, not later because later it is fairly simple I think.

Almard — at the time, by inspection, and palpation, and so forth. Are these methods adequate to determine whether actual freezing has occurred? One technique which cannot be applied clinically is the one now being used experimentally by Dr Meryman * This consists in placing the living tissue between two plates of a condenser and measuring the electrical capacity What he measures is not, as I understand it, the capacitance of the cell membrane, but the change in the dielectric constant of the water, as there is a distinct d fference in this property of water in the liquid as compared with the frozen state There is a sharp end point when freezing is complete so that this method may be a useful tool in experimental freezing of tissue since t can tell the observer whether actual freezing has occurred and what the time course of the freezing process is

By palpation the tissue may feel hard and by inspection it may appear white, but are these criteria enough to permit us to say the tissue is frozen? Might it not indicate instead merely a change in the physical characteristics of the tissue fat together with a constriction of the cutaneous capillary bed and venous plexus?

It is important to establish whether frozen tissues ever recover I think it has been demonstrated experimentally that small fragments of tissue may recover, but whether large areas of tissue frozen slowly under field conditions to the point where ice crystals exist is another matter and clinically of greater importance

I think we all agree with Dr Shumacker that cold injury can occur

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* Personal communication.

without actual freezing I think there is no doubt of that, but I think there is a question

Talbott The sequelae of cold occur

Minard Well, is necrosis inevitable where actual freezing has occurred?

Talbott If there is freezing, then there is the possibility of restoration to the extent that one cannot detect any obvious necrosis.

Minard Yes I do not believe it has been established that tissue actually frozen can recover to any significant extent.

Barton At the Bethesda Conference six weeks ago I heard M. O from Korea He stated that in his opinion and experience, where there was definite evidence that the tissue had been frozen, as when the whole limb was encased in ice there was no chance of recovering that tissue

Talbott I think Colonel Blair was the Medical Officer from Korea

Blair It was asked what evidence there was of actual freezing occurring as compared to the trophic changes we see in trench foot. Evidence put forth by medical officers in Korea was thus they never knew for certain, after examining a foot a day or longer after thawing, whether there had been cold induced trophic changes or true freeze injury but diagnosis of frostbite was often made on the basis of the history that when the soldier first reported for medical care the footwear was frozen to the feet, and could not be removed until thawed off layer by layer down to the skin In such a case they felt they had sufficient evidence to make a definite diagnosis of frostbite rather than trench foot, where there is rarely freezing of the footwear to the feet.

Barton Did he not say that in such cases his feeling was that there was no chance of recovery of that tissue?

Blair I think that in cases where that occurred there was gangrene of large areas of tissue, but I do not believe it was correct to say that there was no possibility of recovery

Mowrey What do you mean by recovery here?

Talbott Colonel Mowrey has seen these cases He has followed them clinically week after week.

Mowrey Most of the cases we have seen have been three weeks old at the time we have seen them. At three weeks after injury you have to assume that the injury was frostbite because there is gangrene there A digit will be black, hard, and mummified yet clinically you cannot tell as to the depth of the destruction, and you cannot tell what regeneration of tissue there will be. Some of these digits are black, mummified, and wrinkled up — I have seen fingers almost like a lead pencil Occasionally over the course of the next two months, I have seen all of this black, dead eschar peel off leaving a baby-pink new skin underneath, normal epithelium.

In others there is no recovery and you have to amputate the finger or toe. Microscopically there is complete necrosis of tissue Clinically though, you cannot tell whether there is superficial or deep gang ene I think it is interesting to note that Larrey (52) one of Napoleon s surgeons made that same observation in his campaign They had frost bite, and could not tell whether it was superficial or deep gang ene The only way I know in which you can tell definitely — and practically it isn t of much use — is with angiography

Barton I did not mean no possibility of recovery from point of iew of the patient. I meant that that particular tissue which had been frozen was done for and had to be sloughed off Of course there might be regeneration. Do you agree that if there has been ice formation in tissue, that tissue is dead and will be sloughed off

Shumacker I disagree

Blair I disagree. I think it is entirely a question of the size and dur tion of the ice crystals. I bel eve there is evidence to show that you cannot lower tissue temperature very far below −2 or −3 C without ice formation occurring Supercooling, in my opinion, is simply lowering temperature of tissue with such tiny ice-crystal formation that f it is re warmed rapidly there is no injury to the cell of gangrene formation I am not convinced — unless you are dealing with the millisecond f eezing to a vitreous state — of slow cooling of an aqueous solution many degrees below its freezing point without producing ice crystals You see super cooling occur only when it is done apidly as in the technique of Sir Thomas Lewis (43) and his group If tissues a e cooled sl wly as we have done in animal experiments at the Army Medical Research Labo ratory we do not see the phenomenon of supercooling For example if rats are cold-exposed at −10 C which is an ambient temperature equivalent to tissue temperature reported reached by supercooling, the tails a e always frozen stiff with subsequent gangrene and tissue loss The same is true of rabbits ears, and in that case we never see supercooling, but always gangrene formation when tissues are lowered appreciably be low freezing temperatures I think that from slow cooling we form la ge ice crystals which destroy the cell and produce gangrene

I have been trying to remember the paper Lieutenant Meryman (53) presented at the National Research Council Conference on Cold Injury some six weeks ago I recall that when he rapidly cooled his solutions be low freezing, he always produced dielectric changes and very small ice crystal formation which were very constant findings if the solutions are then rapidly rewarmed, the ice crystals do not increase in size If one takes animals, and leaves them at very low temperatures f a long period of time to produce f eeze injury and then thaws slowly there is large ice-crystal formation and cell injury I believe that when one speaks

of supercooling, one is not speaking of cooling without freezing, but rather of cooling below freezing with formation of very minute ice particles I think that when one cools an aqueous solution appreciably below its freezing point, one produces ice crystals in that solution, except possibly in the case of millisecond freezing of the cornea, as mentioned by Dr Shumacker

I believe that recovery of the frozen tissue depends upon the size and duration of the ice crystals formed

Mowrey I believe Dr Talbott will agree with me that many of the injured had a foot that was a solid cake of ice. It was necessary to thaw the ice off and most of those cases did develop gangrene either of superficial or of deep extent. However I have seen at least half a dozen of those whose feet were encased in ice, and who had to thaw the ice off, who developed only blister formation, and never went on to complete gangrene, either superficial or deep I have seen that happen, although I think the majority of the ones that had their feet frozen in a block of ice did develop what we call either third or fourth-degree frostbite

Kark I recall seeing, when I was a boy two eels dropped in liquid air Both were taken out, frozen solid One was hit with a hammer and shattered like a piece of glass. The other was dropped in a bucket of water and recovered and swam around I also remember hearing that Greene, the Everest mountaineer put his hand in liquid air Some fingers were frozen solid He pulled his hand out, and there was no residue of damage left at all after thawing Is that right?

Edholm I am afraid I don t know

Kark I think you ought to look that up I recall hearing it during the war He is the kind of man who would do it.

Burton That is the same as the system of freezing in the food industry

Siple I believe we could attack this problem of tissue viability related to quick or slow freezing from another angle by considering the effect of freezing solutions and colloids We know that when a colloid is frozen the elements frequently tend to separate by crystal fractionation. Such a process is currently used commercially to concentrate milk by freezing. I am certain we have all seen frozen milk in a bottle, and noted that pure ice crystals have separated from the milk substitutes These crystals can be removed, leaving concentrated milk in the bottle Again, we will recall that in freezing sea water slowly the salt content is separated If sea ice forms quickly and there is not time for complete separation, little particles of salt will be occluded in a matrix of pure ice. In old sailing-ship days it was a common practice in the polar regions to gather ice from the sea for making drinking water Generally ice more than one season old was selected because it was known that the salt in quickly frozen ice would in due time separate because of its lower freezing point thus pro-

ducing almost completely fresh water When sea ice is frozen slowly ice crystals grow as they do in a bottle of milk, and the salt concentrates and drains out.

Another common example is the formation of crystalline rocks from igneous material. If lava is ejected from a volcano so that it cools very rapidly it forms volcanic glass or a fine grained pumice of homogeneous mixture. If it cools more slowly it forms distinct crystals of the various minerals from which the igneous material is composed. The mineral of the lowest melting point forms a matrix, and is last to become solid. The size of crystals in granite, for example, depends upon the slowness in cooling If cooling is extremely slow as in the case of pegmatite intrusions, crystals many feet in diameter may separate out of the molten solution.

If we consider the freezing of colloids within cellular tissue we can assume that this same process holds true that is if the colloids in a tissue freeze slowly there will be a fractionation or crystal separation of the colloid content. Upon thawing, the colloid nature may in many cases be destroyed owing to agglutination, precipitation, or destruction of surface charges essential to maintenance of the colloid. Therefore we could assume the colloid has been destroyed and that the cell would be dead. On the other hand, if the colloid were frozen quickly there would not be time for the molecules of water and other freezing substances to crystallize and fractionate instead one might picture that the individual molecules freeze in place if they existed in the colloid state. Therefore, upon quick thawing the colloid substances would be in the same orientation in which they were originally and therefore the colloid of the cell could immediately start freezing again, and the cell would still live.

I do not profess sufficient knowledge concerning the freezing of colloids to know how much of my conjecture in respect to animal tissue is proven fact. However if this avenue has not been sufficiently investigated it suggests desirable experimentation along this line

Recalling Dr Edholm s original question as to the recognition of frozen tissue as Dr Burton commented t appears that we may be dealing with an unusual form of ice that forms by quick f eezing in cells We might think of it as a honeycomb structure rather than as solid ice crystals The minute interspersed ice crystals among the protein molecules of the cell colloid may be cushioned so that their expansion force upon freezing is dissipated and the pressure is not great enough to burst the cell walls, whereas larger ice crystals uncushioned would express the tremendous expansion force with which we are well acquainted, and which, even in relatively small-sized crystals, could easily break through cell walls In my Antarctic wind chill measurements I had the problem of preventing the ice which formed by freezing water in a plastic cylinder from breaking

the container (46) I accomplished this by including a cork in the center of the water mass around a portion of the temperature recording element. The expansion force of freezing was absorbed by this cork, and the cylinder was not ruptured by repeated freezing and thawing In a similar manner I postulate that the nonwater substances of the cellular colloids may serve to absorb the expansion force of dispersed minute ice crystals upon formation, whereas in more complete crystal separation and fractionation where larger crystals form, the expansion force cannot be cushioned sufficiently to prevent breakdown of cell wall boundaries

I have found that my concept, although spontaneous with me, is not a new conjecture It appears that the plant physiologists have made greater headway in this general direction than have the human physiologists to wit I submit reference to a publication summarizing numerous references to investigation of death of plant tissue by freezing, involving consideration of the breakdown of colloid structure by freezing (54)

Lewis I should like to ask Dr Shumacker whether the cornea of which he spoke lived

Shumacker I do not know about the cornea. I do not even know whether efforts at transplantation or reimplantation were made The skin, as far as I know did live during the several months of observation. How long these observations concerning survival of the reimplanted skin have been carried on I do not know

Lewis That is the important question Does it live? You are probably familiar with Gross and Peirce s (55) work in Boston on aorta transplants They would take the frozen area and dump it in carbon dioxide and alcohol fifty fifty which is −70 C and they had failures It sloughed out. So now they preserve at +1 and +4 C and have good luck. I *am not convinced the size of crystals has anything to do with* necrosis of tissue

Shumacker Of course Dr Gross and his associates and Dr Hufnagel have been working with the problem of the preservation and transplantation of homologous grafts and homologous grafts do not live. One can transfer them successfully from one animal to another and they may function well and look grossly viable If one examines them microscopically however one finds convincing evidence of degeneration and fibrous replacement by the host

My associates and I have recently begun a study which should give some new information regarding this problem. We are exposing the carotid arteries of dogs, excluding a segment momentarily by placing two rubber shod clamps across the vessel several centimeters apart packing off the adjacent tissue so as to avoid injury to it, and then freezing the artery solidly with an ethyl chloride spray The clamps are then removed and the wound closed These experiments have not been completed but I

think I can safely say that, though the arteries appear grossly to survive and though they continue to function well, microscopic studies indicate that their cellular structure is pretty completely disintegrated by the injury and that the surviving vessel is largely a structure built up by fibrous replacement. We are also studying the effect of f eezing upon other isolated but intact tissues — for example the sciatic nerve Thus far these studies seem to indicate that such injuries to the sciatic nerve tend to be followed by a paralysis lasting a period comparable to that which follows surgical crushing of the nerve at the same level. We are also studying wound healing and the gain in tensile strength of incised wounds made through skin immediately after it has been frozen solid and allowed to thaw

Horvath In the blood-substitutes program they are trying to save the red-cell residue from blood collected by the Red Cross There have been very nice experiments by a chap down at Bryn Mawr which show that very rapid freezing is a fairly excellent way of preserving the red ells If you rethaw them rapidly you have at least about 80 or 90 per cent viable ed cells which will go through their normal span of about 1?0 days The few which apparently do not survive are those which may be in the deeper part of the mass and there you have the problem of rupture of the cell, which does occur if you freeze the red cells very slowly

Behnke To get back to one of the fundamental questions proposed by Dr Shumacker concerning the applicability of the nimal experimental work to human beings Are the experiments in which the animal tissues are frozen rapidly at all applicable to the problems that human beings a e confronted with in frostbite? Second, do we have any graphs showing the susceptibility of various tissues in terms of temperature time to injury For example Dr Gottschalk mentioned the value of 7 to 8 C which is certainly capable of producing injury to tissues in water exposures of one-hour duration. What is injured I do not know — perhaps the nerves Now what is the critical temperature w th expect to injury f various tissues in relation to time, and e we simulating the conditions or temperatures and the time elationships in experiments on lower animals?

Shumacker May I respond to part of that question I believe that these experiments are applicable to human frostbite, at least t the problem of gangrene.

Talbott Do you refer to the thin-slice experiments

Shumacker No I am speaking of the fairly rapid f eezing of whole parts, like the leg nd foot, ear or ta l I believe that these studies are applicable because I believe that it is true that comparable quick freezing in high-altitude frostbite produces an injury in man quite similar to that which develops much more slowly in ordinary ground-type frostbite As I mentioned earlier I feel that the ecent demonstration in Colonel Blair s

laboratory that experimental frostbite can be produced more gradually by exposure for a longer time to low ambient temperatures provides us with a new valuable tool If it can be shown that this type of experimental frostbite responds to such measures as rapid thawing in a comparable manner to the response of the more rapidly produced experimental immersion frostbite injuries, additional support will have been furnished for the applicability of the experimental work thus far carried out.

Blair We have produced slow cold injury by exposure of a series of animals to dry cold over a long period of time

Gottschalk Is this a matter of hours or days?

Blair That is over a period of about twenty four hours. We try to make exposure periods comparable to field conditions for troops. In some cases there have been two or three days of cold exposure, but usually a period of from six to twenty four hours exposure to a dry atmosphere that will just produce freeze injury is sufficient. We cannot tell gross difference in the lesions from immersion and those of dry-cold exposure.

However before we can be sure there is no difference, there will have to be histological studies and also evaluation of response to various therapeutic procedures, such as types of thawing and utilization of drugs, to see if identical response is observed for the same degree both of slow-freeze and of quick freeze cold injuries If there is any difference in the two, then it is in two aspects that I can find from literature and discussion. One trophic changes are more apparent clinically in trench foot and two, in trench foot there is a more marked systemic reaction and more severe sequelae *In the quick freeze type of cold injury one may have* considerable involvement without any systemic reaction. Experimentally Meryman s investigations show there is a difference in dielectric measurements and size of ice crystals of a frozen solution, depending, first, on the rate at which it is frozen, and second, the rate of thawing. Whether it has any practical significance clinically I do not know Grossly we can tell no difference at all.

Horvath Some experiments we carried out with the Army Chemical Service on this very same problem indicated that with slow freezing, −30 C., for about six hours, you did have the same type of frostbite. When rats were placed in hot water at about 50 or 60° C., you did not have as much gangrene develop as you did when you allowed the animal to warm up at room temperature. Of course, it is hard to tell whether or not they would have received the same amount of injury if you had warmed them up fast, but it seems as though rapid rewarming was of some benefit even in that type of cold injury

Mourey I think there are two factors clinically which we must not lose sight of in our animal experimentation One is the question of constriction from tight fitting clothing, and so forth that enters into the human

cold injuries and the other is the question of moisture Clinically many of the patients that we see with frostbite were exposed to temperatures between 20 and 30 below zero F However many of them were exposures of around 10 below zero F Almost invariably with that type we discovered that he had been walking a great deal, that he had been perspiring considerably that he had not changed socks, and that he had not changed inner soles in his combat boots It is a question of moisture as it was with original trench foot in World War II

I know Dr Talbott saw one patient that we had from Alaska He had been on a snowshoe march in Alaska in which about two hundred troops participated. Two or three got frostbite in their face or ears but he was the only one that had frostbite in his feet. He came into the hospital with gangrene of one foot. His story was very clear On one foot he had had trouble with his snowshoe strap coming unfastened. On the other where his strap was very tight, he had had no trouble The foot on which the strap didn t come unfastened, and on which it stayed tight, was the only foot he froze. The other one was perfectly normal This illustrates the element of cold plus constriction

Horvath There is another point that may be brought out. Perhaps Dr Burton can provide the answer Take an animal with mass A and freeze a mass of tissue B then take another animal with mass C $(A + X)$ and freeze the same mass of tissue as in B What comparison can we make between the two? There is certainly going to be some influence on the residual mass which is not being exposed to this cooling

Burton More important is the circulation. I should like to raise this point at this place namely the vasomoto change The circulation is important in determining the transfer of heat from the rest of the body and here the mass comes in. This is a very important point when we re discussing whether or not animal experiments can tell us what happens in the human being

Dr. Edholm may correct me on this, but I do not know of any animal experiments which have shown that the hunting phenomenon, which Sir Thomas Lewis, I think, discovered, and which has been worked on since by Dr Greenfield and by Dr Edholm, occurs in animals say in a dog s leg. After all it is this hunting phenomenon that seems to provide a protection to the tissues This reaction will affect very much the incidence of freezing and the conditions which will produce it in the human digits. If the animals do not have this hunting reaction, then it means there is a very profound difference, and it will affect the interpretation of our experiments on animals

I should like to know whether there has been any work on animals limbs to show that an animal has this phenomenon which is generally called now I think, the hunting reaction Do you know Dr Edholm?

Blair I might mention some experiments which I hope to report on later We do have what appears to be at least a very strong indication of the presence in animals of this hunting reaction of Lewis (56) It apparently must play a part and probably an important part in animal protection against cold injury I think the hunting reaction does occur in animals in a very similar manner to that in humans

Edholm Grant and Bland showed that cold vasodilatation occurred in the rabbit s ear and also in pads of birds (57 58)

Burton I have tried it recently in the isolated perfused rabbit ear which stays very well as judged by its response to adrenalin, for eight hours The hunting reaction absolutely isn't there We were investigating the blood flow against the temperature of the ear and were looking for this reaction, but could find no trace of it in the isolated ear

Blair I might mention that in the intact animal the suggestive evidence is thus If rabbits that have been cold-acclimatized over a long period of time (seven weeks) and rabbits that have never been exposed to cold are both placed in a cold room at a low temperature (—45° C.) the nonacclimatized rabbits develop frostbitten ears even though their colonic temperatures are no lower than those of the cold acclimatized rabbits whose ears remain completely normal For protective purposes there have been no gross anatomical changes in the ears, such as increased fat deposition or increased furring Likewise, no general hypothermia is present when the nonacclimatized rabbits ears freeze. We feel that one of the most likely changes giving added protection against cold injury of cold acclimatized rabbits ears may be a stimulation or conditioning of the hunting reaction by the acclimatization process Thus, the hunting reaction in the cold acclimatized rabbit may have become quite active and highly protective against cold injury while in the nonacclimatized rabbit it may be so weak or underdeveloped as to provide little or no protection against frostbite

Burton That should show in your skin temperatures, should it not?

Blair Yes but we do not have very good continuous records of ear temperatures, which we still hope to get It should show up also in plethysmographic readings which we plan to do on rabbits ears provided Dr Burch can suggest some way of adapting the plethysmograph cup to the rabbit s ear

Talbott How long does the hunting phenomenon persist with continued cooling?

Blair We have carried out cooling experiments on human subjects and observed the hunting phenomenon Dr Gottschalk will recall these tests We had a group of seven subjects on whom we were studying cooling rates of the feet During four hours exposure at —30 C., the skin temperature falls to around 1 or 2 C. Our asso[illegible] tell us

we were going to get those boys into trouble by freezing their feet. Then, with the foot temperature at 1° or 2° C., and with no activity on the part of the subject, the foot would suddenly warm up to 5° or 6° C. This pattern of cooling and spontaneous rewarming occurred several times during four hours exposure at −30° C. The feet would cool nearly to freezing but at the critical point rewarm spontaneously — the typical hunting reaction.

Horvath How often does that occur? In what percentage of your subjects did you find that?

Blair We observed the hunting reaction in the majority of our seven subjects, and it occurred rhythmically approximately every fifteen to twenty minutes.

Siple Did you get any correlation with muscle tenseness

Blair We have no measurements on that.

Edholm I hope we do have a discussion on the hunting phenomenon. Perhaps that will come later when we discuss human work (41-59).

Talbott Dr Edholm, we are not going to spend much time in so far as the agenda is concerned, on human studies. If you have anything that you would like to present on human work, I suggest that you do it presently.

Edholm If it is not taking away too much time. We haven't heard very much about the animal studies.

Talbott We are going to continue through the afternoon on animal studies.

Edholm As far as the work which has been done in Britain is concerned, this has largely been carried out by Dr Greenfield and his associates in Belfast (60–64). Both his group and mine have chiefly been studying the circulation in the hand when it's immersed in cold water.

Although the hunting phenomenon is best displayed when the hand is in ice water, it can be observed also when the hand is exposed to cold air. The first point to be made as a result of Greenfield's work, is that hunting is apparently not due to an axon reflex. Hunting was originally used to describe the fluctuating rise and fall of skin temperature of fingers immersed in ice and water, a more or less rhythmic series of vasodilatation and vasoconstriction. I think first of all one should be interested in the vasodilatation. When you expose your finger or hand to water temperatures of 0° to 6° C., there is an immediate vasoconstriction, so far as we can see there may be virtually no blood flow at all for a period which may last as long as five minutes. Then there is a very sudden vasodilatation, and that phenomenon of vasodilatation can and does occur in subjects who have their fingers completely denervated, or who have had their vasomotor supply blocked. However, in the completely denervated ex

tremity (and this has only just been reported by Greenfield and others) the vasodilatation is not quite the same as in the normally innervated finger in that it can be modified by the pretreatment of the extremity In the normal subject, with intact innervation, if you immerse the hand first of all in water at 15 C. or 30 C. or 45 C., it does not affect the subsequent vasodilatation when the hand is exposed to water at a temperature of 0 to 5 C.

The denervated finger when it is pre-cooled in water at 15 C. and is then put into ice water does not vasodilate If you have the denervated extremity first of all in water at a temperature of 30 C., on immersion in ice water you do get a vasodilatation which is less than on the innervated side But if you pre-heat the denervated finger in water at 40 C. to 45 C. and then cool in ice water there is a vasodilatation which is equal to that on the normally innervated side or may be even greater So the vasodilatation due to cold can occur in the complete absence of any nerve supply but it is modified by the absence of that nerve supply

The hunting phenomenon itself that is, the periodic vasoconstriction and vasodilatation, can also occur in the complete absence of any nerve supply The hunting phenomenon is a very variable phenomenon in our experience, that is to say you cannot state that there will be a rhythm of vasodilatation and vasoconstriction lasting so many minutes in any one particular subject. You may get periods of ten, twenty or thirty minutes with no obvious hunting in the sense of a vasoconstriction coming in on the vasodilatation at all. The immersed part may stay completely vasodilated for the whole time of exposure.

Talbott That is what temperature again?

Edholm This occurs when you are exposing the extremity to water temperatures in the range of 0 to 6 C.

The third point is that hunting appears to occur independently in the different fingers For example, if you have the whole hand in water one finger may constrict, and others remain dilated. Then this one will dilate, and perhaps another finger will constrict and then dilate. The hunting, in other words, is not a generalized phenomenon in the sense of the constriction affecting the whole of the part which is immersed. It occurs at different times in different fingers even though they are all exposed simultaneously

So the mechanism of the dilatation and the mechanism of the constriction, although modified by nerve supply can occur independently of it. But what the mechanism of the dilatation and constriction is, I do not think we can say at present.

Blair We have not studied individual fingers or toes, but we have observed in the feet that the hunting reaction may show a different rhythm

or pattern in one foot as compared to the other For example, the right foot may be in a state of vasoconstriction at the same time that the left is in a state of vasodilatation.

Barcb Have you studied any abnormal states?

Edholm Greenfield has studied two subjects* with peripheral vascular disease in which he also got this vasodilatation, but that is all that has been done so far as I know

Shumacker Dr Edholm, do you have any data upon the various components of digital or hand circulation? Are you able to compartmentalize the circulatory changes with respect to capillary circulation, flow through arteriovenous shunts, flow through the larger arteries, and so forth?

Edholm I think one should emphasize the very great extent of the vasodilatation with cold. Most of the studies have been done using a calorimeter rather than a plethysmograph, for this reason, that Greenfield found initially that when he was studying the flow with a plethysmograph he was unable to obtain records which he could interpret in the vasodilated phase. When venous occlusion is applied, you may get only half or at most one pulse-beat rise in volume in the finger volume So it is virtually impossible to draw a line that would mean anything at all as regards the interpretation of the actual flow rate However if you use a calorimeter which with all its disadvantages, with all the assumptions one has to make to calculate quantitatively one can at any rate determine the minimum flow that must have occurred under those conditions.

Now just as with the hand immersed in hot water so with the hand in cold water there is very definitely a bigger flow in the distal part of the digit than in the proximal, and the flows in the digits are higher there than in the body of the hand There is the usual gradient of flow rate from the terminal portion of the finger up to the hand itself I think that suggests that the A V shunts are involved but we cannot say any more than that.

Talbott We will have an opportunity to continue this discussion in the afternoon session when Dr Crismon will lead off the discussion. The subject matter will be the same as that of this morning Dr Burton raised one question which I think should be amplified, or rather the answer to his question should be amplified Is this Conference interested only in the Macy Foundation sponsoring animal experimentation and is it opposed to the discussion of clinical problems Of course the answer is no

Burton The idea prompting the question is that which implies that fundamental physiology can be done only on animals. I feel strongly that fundamental physiology can be done just as well on human beings.

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* Not yet published.

Fremont Smith I wholeheartedly agree The fact that we are working on animals was not in any way intended to make it fundamental. We wanted to stress the physiological-biochemical physical aspects of the problem, whether it concerned human beings or other animals.

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ANIMAL STUDIES

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DR. SHUMACKER HAS raised some interesting questions regarding the reversibility of cold injury We have to consider the effects of temperature per se as distinguished from other events that occur with freezing temperatures or with temperatures short of freezing These questions include points that have already been discussed to some extent the matter of crystal formation is important the role of ischemia itself has been touched upon but not yet dealt with very extensively

It has been most unfortunate that nearly all the research that has been carried out on cold injury has been under the driving urgency to find a method of treatment or prevention, and much of the fundamental work that might have contributed to our understanding of the nature of cold injury has gone by the board because there wasn t time for it. We had to employ empirical methods, and it is only now that we are catching up a bit to interpret some of the things that were discovered empirically

To distinguish partly between the effects of temperature itself as an injury factor and a factor secondary to low temperature, we might look at some of the work that has come from fundamental investigations on isolated tissues as well as the fundamental work that has been done on hypothermia in animals It is well known that certain animals are able to achieve very low body temperatures during hibernation (1) and even nonhibernating mammals can be cooled to temperatures well below their normal body temperature and then brought back by one means or another either rapid warming or slow warming (2) If their temperature is not lowered too drastically for too long a time, these animals may be rewarmed and show no evidence of permanent damage that group of animals includes man, as you know

As far as work on isolated tissue is concerned, the examples of it that I have available are somewhat limited and include work that was done in the physiology laboratories at Stanford, at first by Dr Fuhrman and Dr Field (3) who did a considerable amount of tissue-respiration study in relation to low temperature.

Data shown in Figure 3 (3) furnish a partial answer to a question raised by Dr Behnke. Here are the results of oxygen-consumption measurements of rat brain cortex and rat kidney tissue The lines connecting open circles in each figure show control data tissues are taken from the animal placed in vessels in the usual way and the oxygen-consumption rate is measured.

The black triangles show data from tissues that were cooled immediately between points *A* and *B* to 0.2 C., maintained at that temperature for well over an hour then rewarmed quickly to 37 5 C., and allowed to resume oxygen consumption. The oxygen-consumption rate was measured in the usual way

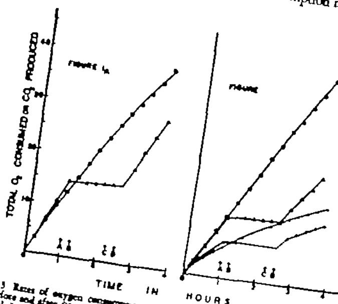


FIGURE 3 Rates of oxygen consumption and anaerobic gly lysis in at brain and kidney slices before and after 90 minutes at 0 2 C Reprinted by pe mi n from Fuhrman F A and Field, J., 2nd *Am J Phy iol* 139 93 (943)

In Figure 3 the section on the left shows the beha r of rat br in cortex with respect to oxygen consumption The sl pe of the line showing the early part of the curve drawn through the triangles is just about the same as the slope of the line found aft ew rm ng This tissue with that interval of cold exposure at that deg ee ppe red to suffer no permanent impairment, that is, no immediately detectabl impairment of its metabolic activity as we judge it f om oxygen-consumption rates.

The section on the right shows two bits of d ta on xygen consumption and anaerobic glycolysis of kidney cortex The open circles show control data the triangles indicate the old tissue and the small dots and x s represent a similar experiment but one in wh h anaerobic glycolysis was measured That too, has approximately the same rate fter cooling as it does before being subjected to 0 C

Data more dramatic than this are available n the literature, I am s re, on tissues that have been subjected to extremes of temper ture far below 0 2 C. Some of it has been cited by Dr Shumacker but there are experi-

ments on mammalian spermatozoa, for example, in which tests of oxygen consumption glycolysis, and viability have been used after the sperm was subjected to temperatures in the neighborhood of −70 C. and lower (4)

In Figure 4 data on a similar experiment (5) are shown for skin taken

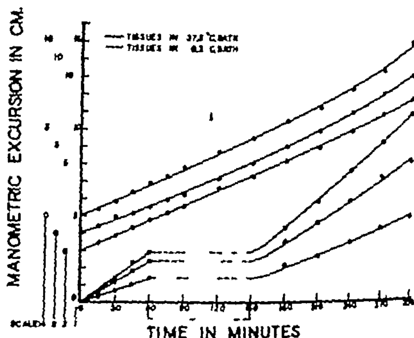


Figure 4. Oxygen consumption of normal rabbit ear skin before and after one hour at 0.2 C., Reprinted by permission from Crismon, J. M., and Field, J. 2nd Final Report OEM CMR Contract 476 (1945)

from the inner surface of the rabbit's ear These skin samples are convenient to use because their thickness is well within the limiting thickness ranges as prescribed by Warburg for tissue oxygen-consumption rates The slopes of the curves in the upper part show control by manometer excursion. The slope of the line yields a value for oxygen consumption as the usual Q_{O_2} The lower three lines present data from samples of skin from the same animal that were subjected to 0.2 C. during the period between 60 and 150 minutes, then rewarmed before oxygen consumption was again measured. Skin samples then are found to behave in the same way as the tissues from brain and kidney that have a much higher oxygen-consumption rate.

Incidentally skin is a peculiar tissue in that it contains relatively small amounts of cellular material compared to structural material in contrast

to other organs studied, and it may be that the things that make skin behave differently with respect to cold exposure depend very markedly on the proportion of structural and cellular material.

When rabbit ear skin is cooled more drastically for example, at −35 C, and is then allowed to thaw at room temperature, its rate of oxygen consumption is so low that it cannot be measured by the Warburg method. I think the maximum that we found was a Q_{O_2} of 0.1 — that is, 0.1 cubic millimeter of oxygen per milligram of tissue per hour.

This action of cold effectively destroys the ability of the tissue to consume oxygen as we measure it by this rather crude method. There may be some cells in that sample of skin that could carry out oxygen consumption if we were able to get them out and measure them. The fact that there are certain maneuvers we can carry out which will lead to the survival of tissue, namely immediate rapid warming, as Dr. Shumacker described, suggests that this may well be so.

In Figure 5 (5) are illustrated some slopes of manometer excursion lines taken from Warburg measurements on control skin samples, frozen

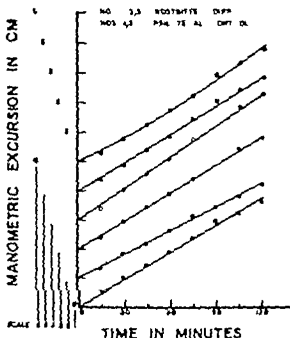


Figure 5. Effect of rapid rewarming on Q_{O_2} of frozen (−35 C for 1 minute) rabbit ear skin. Reproduced by permission from Crismon, J. M. and Fuhrman, F. A. 2nd *Final R* part OEM CMR Contract 476 (1945)

skin and frozen skin after rewarming Samples from uninjured ears, samples from ears that were immersed while they were attached to the rabbit in freezing mixtures at −55 C. for one minute, and then immediately afterward rewarmed rapidly without intervening thawing in water at 42 are included. Tissues represented here as numbers 1 2, and 3 (the lower three curves) were from ears subjected to freezing and then dipped in warm water before samples of skin were taken and put in the Warburg vessels These samples of tissue consumed oxygen at about the same rate as skin taken from the ear that was not injured in any way

The frozen state itself under these conditions, appears not to be injurious the events that go on during the period of thawing, if thawing is allowed to occur at room temperature, appear to injure the tissue.

We have no information, other than some observations of transilluminated ears under the microscope, which tells us anything about details of events after thawing If you look at an ear that has been frozen in a freezing mixture of −55 C. as soon as you can get it under the microscope you will see that the tissue is opaque. From what has been said this morning, I judge that its opacity depends upon the presence of ice crystals. Within a very few minutes, when thawing occurs, enough light gets through the ear to permit you to make out some details of vascular structure. Soon after that the phase of hyperemia begins, and good blood flow can be seen at least for a brief interval



FIGURE 6 One ear of each rabbit was frozen for 1 minute at −55 C. Animal 16C ... treated by immediate rapid warming at +42 C. Photographed at 3 to 4 weeks after injury Reprinted by permission from Crismon, J M and Fuhrman, J 2nd *Final Report OEM CMR Contract 476* (1945)

I think that possibly the work that Dr Meryman has carried out, and perhaps also that of Dr Lewis, will give us the first clues as to physical details responsible for events that we have described empirically and for the metabolic events that we have measured to some extent.

Next I should like to deal briefly with the role of blood flow changes in cold injury. We have to do here with changes that regularly go through stages of hyperemia, edema, stasis, and finally arrest of the circulation, if the injury is severe enough.

In the next four slides are illustrated the changes that are seen.

Figure 6 illustrates the appearance of a rabbit's ear that was dipped in warm water after freezing, and compares it with the loss of tissue in the untreated animal. Animal 16-C had the ear dipped in water at 42 C immediately after freezing at −55 C. for one minute. The other animal was not treated. These photographs were taken some three to four weeks after injury. Notice that the ear that survived the injury is shrunken, but it shows intact epithelium over its surface and good hair growth over the injured region. At one time this ear was completely denuded of hair.

Figures 7 and 8 illustrate the changes in rabbits' feet after frostbite. The time intervals in the following group vary from three hours to ten days. Hyperemia, immediate swelling and wet gangrene, followed by dry gangrene, are shown.

Figure 9 was photographed two to three days after frostbite.

The foot shown on the right of Figure 10 is in the stage of wet gangrene six days after injury. The other foot is completely dry and shrunken. The line of demarcation is quite clear. Separation of mummified parts of these injured feet depends upon activity of the animal and the roughness of the cage in which it is kept. One of those shown was in a wire-bottom cage and the other in a smooth-bottomed cage.

In analyzing the nature and magnitude of the edema that occurs after cold injury we have studied the relative volume of the foot with time, the composition of the edema fluid and the pressure achieved in the tissues during maximum swelling.

Figure 11 (6) illustrates the rate and magnitude of swelling plotted in terms of relative foot volume.

The feet were measured up to the line of immersion in the freezing bath. When they were remeasured by displacement in a graduated cylinder the same reference point was used. Over the first six hours the swelling reaches its maximum. Three general groups shown on the graph include some that were frozen for one minute, two minutes, and three minutes at −55 C. As you can see with these three degrees of injury the amount of swelling of the foot is approximately the same although there is much greater range of variability in the briefer periods of immersion.



FIGURE 7 and FIGURE 8. Rabbits' feet 5 and 17 hours after frostbite (3 minutes at −55 C.) Reprinted by permission from Crismon, J. M. and Fuhrman, F. A. 2nd *Final Report OEM CMR Contract 476* (1945)

Injuries are relatively inconstant in the group subjected to one-minute exposure. Most of these animals lose no more than portions of toes, or entire toes, whereas those that were exposed for three minutes lost either all of the foot up to the point of immersion, or retained a small pad of tissue on the plantar surface.

Figure 12 (6) shows the protein content of edema fluid from these animals. In the early phases, when edema had first formed, it had just about as much protein in it as the plasma. We have not made detailed analyses of the protein to be sure that it is all plasma protein. After injury the protein concentration in the edema fluid goes down. This is in

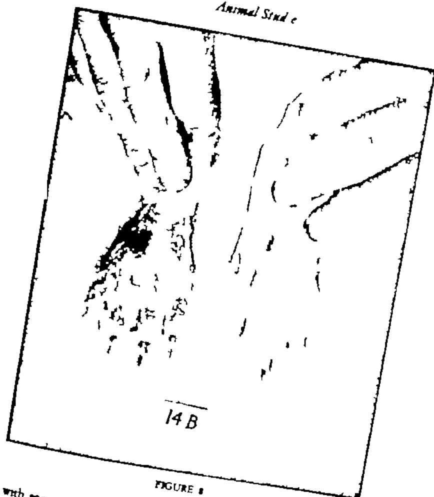


FIGURE 8

I ing with some observations of E E P chir wh stud ed edema fluid after ischemic injury in rabbits (7) I think he stud ed fluid both from ears and from feet. In his experiment th ischemia g e rise to swelling of the part, and in early phases the edema flu d was high in protein it later became much more dilute

This material, as well as evidence fr m other laboratories on lymph flow following burns (8) and on rates of dye movement in lymphatic vessels from our own laboratory (6) suggest that the late eduction of protein concentration involves a decreased r te of los of p otein from vessels coupled with a continuous production of fluid from the blood flow that persists.

Figure 13 (6) shows the interstitial fluid pressure related to relative

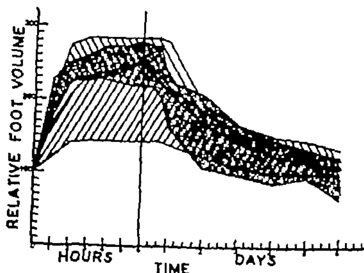


FIGURE 11 Comparison of volume changes in rabbit feet after exposure at −35 C. for one, two, and three minutes. Reprinted by permission from Fuhrman, F A., and Crismon, J. M.: *J Clin. Investigation* 26, 245 (1947)

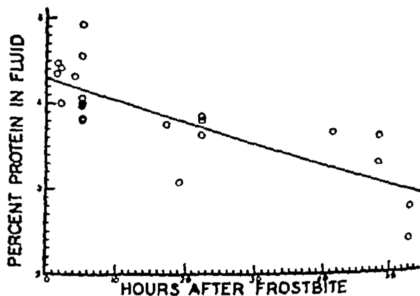


FIGURE 12. Time course of change in protein concentration of ear-blister fluid following severe cold injury Reprinted by permission from Fuhrman, F A., and Crismon, J. M *J Clin. Investigation* 26, 245 (1947)

Crismon As edema fluid accumulates in the tissues, certain vessels are changed in their mechanical relationships one with another so that kinking occurs in some of them, and in those vessels that become kinked, flow stops.

Fremont-Smith Wasn't you have slowing of the flow throughout from the compression of venules?

Crismon I wasn't able to continue observations long enough to determine that. As soon as the tissue thickens with accumulating edema,

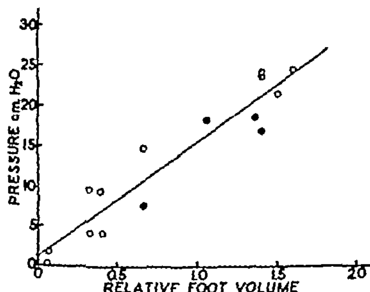


FIGURE 13. Relationship between foot volume and subcutaneous tissue pressure after frost bite. Reprinted by permission from Fuhrman, F. A. and Crismon, J. M. *J. Clin. Investig.* 26, 241 (1947)

it becomes very difficult to see through and I do not have enough information on that.

Fremont Smith That would be consistent with the general theoretical concept of the mechanics, wouldn't it? That is, if you put a limb under pressure, the compression would be felt first on the vessels at lowest pressure, which would be the veins and venules and the compression would increase the resistance of flow and diminish the greater flow

Crismon: Yes. With the perfusion pressure coming in from the arterial side, it doesn't take very long to raise pressure in the capillaries, and hence in the collecting venules, to the point where pressure changes are communicated through the system.

Fremont Smith The flow continues, but continues at a lower rate, doesn t it?

Crismon No it does slow down, but I am not sure it slows down *because of the accumulation* of edema fluid or after accumulation. None of our measurements would permit us to say that we simply do not have data of that kind

Fremont Smith I just wanted to make the point that, on theoretical grounds, if you subject any collapsible tube with fluid going through it to external compression which is sufficiently great to approximate the lowest pressure level in the collapsible tube, although flow will continue because of the build-up of pressure, the rate of flow will be slowed because of the increased peripheral resistance.

Crismon That would be true if you modify your statement to include regional narrowing If the change is uniform throughout, I do not see that it would make any particular difference in flow rates. Dr Burton would be able to comment.

Burton It does slow it down, yes, but proportionately It is the difference of pressure between the inside of the vessels and the tissues that matters The size of the vessel decreases in proportion to that transmural pressure, so the vessel has become smaller We have experiments on putting tissue pressure on the human arm. Flow does decrease with increase of tissue pressure

Crismon That is the point I wanted to make.

The thing that made me hesitate was the observation of Glenn and Drinker (8) that lymph-flow rates are greatly accelerated in burned tissue where edema reaches large magnitude You would expect that rising pressure there would reduce the flow of lymph

Fremont Smith The point is that you have a new inflow which is an entirely different story

Crismon We have evidence of increased lymph flow too, in this experiment

Fremont Smith I mean the source of the lymph fluid you have new sources of lymph fluid that have been opened up by capillary visibility It is as if you had inserted many needles into the tissue and poured lymph in. I should be interested to know if Dr Burton or anyone else would want to make a comment that the increased rate of lymph flow in burns or in this type of injury will give you any indication of the rate of blood flow I don t think it would. I think that the blood flow could regularly be decreased while the inflow is increased

Talbott Does that produce the reverse effect?

Crismon I think that is correct.

Burch Don t you think there is another factor which should be considered? When a part such as a fingertip swells, the skin pulls away and

by means of trabeculae and fibrous tissue which connect the skin and the blood vessel it may actually open the vessels thus vessels may be made more patent. This is true in the lymphatics in the cardiac edema where the tissue pressure rises while the lymphatics actually become extremely dilated, in fact, so dilated that even the valves fail to function, becoming insufficient. That is considered to be due to the stretching outward of the skin, pulling these connective tissue fibers or other connecting structures between the surface of the wall of the lymphatics and the surrounding skin.

Fremont Smith Would that apply to the blood vessels?

Burch I am inclined to believe that such a concept should be considered, at least.

Fremont Smith Did you have any evidence in your case that your blood flow was increased? It is usually decreased, is it not?

Burch We did not measure blood flow in our own studies, only tissue pressure

Almard I believe, Dr Fremont Smith, that there are some recent reports from Cope's laboratory (11) in which both lymph flow and arterial inflow was measured following freezing in the feet of dogs A rather surprising finding was that during the period of rapid swelling and rapid lymph flow that occur on thawing, there was no striking fall in arterial inflow

Fremont Smith Oliver Cope?

Almard Oliver Cope yes sir

Fremont Smith The only point I was trying to make was that other things being equal, the mechanical compression of a limb with elastic tubes in it with fluid flowing through them would tend to slow the blood flow Now the blood flow may be maintained by a variety of factors and if you had sufficient vascular arteriolar and arterial dilatation which would be like turning on the faucet of your garden hose to a large extent, you could compensate for the slowing tendency and conceivably even get an increase in flow but that would be a secondary compensation to vascular arterial dilatation throughout and above the area involved.

I think I am right in saying that mechanical compression from without upon elastic blood vessels, other things being equal, would inevitably tend to slow the flow through that system if the pressure reached the level of the lowest pressure within the vascular system

Burton I can give you the actual figures on the human arm. In low vasomotor tone in the dilated state a rise of tissue pressure of 20 mm. would decrease the flow by about 20 per cent On the other hand, in high vasomotor tone in a constricted arm 20 mm tissue pressure may stop the flow altogether

Fremont Smith Supposing you apply heat so that you get a vascular

dilatation or histamine, could you not again increase the flow through the one that had been reduced by 20 per cent?

Burton You would if you left the tissue pressure on.

Fremont Smith That, I think, is the situation that Cope is probably dealing with in his situation there was a vascular dilatation of the arterial tree which compensated for the external pressure.

Minard There is also the question of whether some of the blood may not be shunted through arteriovenous anastomoses

Kirk What about damage to elastic tissues? In other words, the stretching of any part of the body by local edema depends upon the ability of the intercellular proteins — collagen, elastin, ground substance — to stretch If these are healthy you can only stretch so far If these same tissue structures are damaged, then you can get local edema even if you don t have increased permeability

Crismon When you watch the tissues under the microscope after thawing and during the phase of hyperemia, you notice a rapid dilatation of all vessels that you see, including venules and capillaries, capillaries in such numbers that you couldn t believe so many vessels could have been there before injury

Fremont Smith Is this in the ear?

Crismon The ear Within ten minutes, stasis in the true capillaries becomes complete with packing of red cells very close together and little or no plasma. Flow persists in other channels for quite a long time.

Fremont Smith Stasis in spite of arteriolar dilatation?

Crismon Yes.

Fremont Smith Not due to arteriolar constriction, in other words.

Crismon No This is stasis that is analogous to that described by Landis (12) in which the cells become packed tightly together by reason of the plasma loss through the walls

Burton Have we other figures on the blood flow during edema phase?

Fremont Smith Does anybody know of that during cold injury? I think that is an interesting point.

Minard Cope s experiments did include cold injury

Burton He has measurements of blood flow?

Minard In the foot

Fremont-Smith Where was that reported?

Talbott In one of the surgical journals There is a series of articles on damage from cold.

Fremont Smith Recently?

Talbott Two years ago

Minard In 1950 I believe.

Crismon I remember one on tourniquet damage by Aub in the *Journal*

of Clinical Investigation somewhat earlier (13) The more gradual closing of the circulation was a factor that was interesting to us. We followed the skin temperature in rabbits ears after injury —

Shumacker May I interrupt to give the reference to Cope's work? It is a paper by Rosenfeld, L., Langohr J L., Owen, C. R., and Cope, O entitled Circulation of blood and lymph in frostbite and influence of therapeutic cold and warmth, and appeared in the *Archives of Surgery* Vol. 59 page 1045 1949

Crismon Measurements of skin temperature in the injured ear show that at least some blood flow persists for a matter of fifty hours or so after injury

Figure 14 (14) shows the temperature changes. The lowest line shows

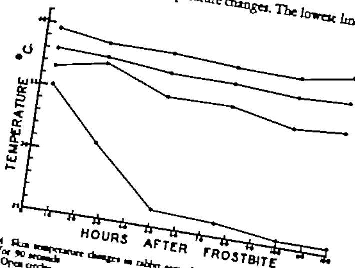


Figure 14 Skin temperature changes in rabbit ears after exposure of distal parts of ears at —55 C for 90 seconds
Open circles — rectal temperature; Unexposed proximal portion of frostbitten ear
Solid circles — Tip of normal ear; Tip of frostbitten ear
Reprinted by permission from Fuhrman, F A and Crismon, J M J Clin Investigation 26, 236 (1947)

the temperature of the injured part of the ear The open circles give the rectal temperatures of the animal the unexposed portion of the frost bitten ear is shown by circles darkened on the right. The temperatures of the tip of the normal ear are put in for comparison.

Fremont Smith What is the environmental temperature?

Crismon It varied little from 25 C. in our laboratory

Fremont Smith So it fell down too

Crismon That is correct. But in the interval including the time of injury and the period of hyperemia, which produced a temperature of 35 C. in the ear that is, within fifty hours, there was gradual decline of temperature. This was our usual experience

Other means of analyzing this gradual change in circulation after injury can be employed. The use of intravenously injected fluorescein permits you to get some idea of equilibrium of interstitial fluid and blood (15 16) If there isn t any fluorescence there at all, the assumption is

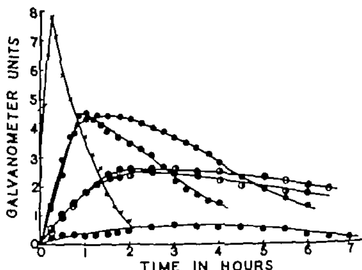


FIGURE 15 Intensity of fluorescence of rabbits ears at different time periods after frostbite. Ears exposed at —55 C. for 90 seconds. Fluorescein injected at zero time.

- X Normal ears (6 animals)
- ⊗ Immediately after frostbite (5 animals)
- ◐ 1 hour after frostbite (4 animals)
- ○ 1 day after frostbite (5 animals)
- ◑ 2 days after frostbite (5 animals)
- ● 3 days after frostbite (2 animals)

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that the blood isn t circulating if it does appear some blood must have brought it there.

More interesting to us was the rate of its removal, because that gave us some idea of the degree of communication between the perivascular tissue fluid and the blood stream.

Figure 15 (16) shows some curves derived from measurements of intensity of fluorescence. The tallest curve connecting crosses shows the

change in fluorescence in normal ears. The intensity reaches its maximum somewhere in the neighborhood of fifteen to twenty minutes, and over the following two hours the fluorescence dies away completely. The measurements of fluorescence intensity were plotted on the ordinates in arbitrary galvanometer units. Barrier-layer photoelectric cells were used.

The other curves represent intensities of fluorescence in injured ears at varying time intervals after frostbite.

Immediately after frostbite the peak of intensity of fluorescence is reached at a later time than that which occurs in normal ears. Total magnitude is less, and it has a more prolonged rate of removal than does that in the normal ear. With increasing time up to three days after injury these differences become more pronounced. A more striking aspect of the change is the relatively slow rate at which fluorescein can be taken out of the ear once it gets in. To us, this meant that there was not only a closing down of the circulation, that is, probably less blood flowing through the ear, but also a reduction in the total area available for exchange between the flowing blood and the perivascular fluid.

This is consistent with what you see under the microscope in the closing of first, true capillaries, later the arterio-venular capillaries, and finally arteriovenous anastomoses, not always in that order.

Burch: Was the edema phenomenon associated with the accumulation of edema fluid and dilution of the fluorescein?

Crismon: To some extent.

Burch: Was it significant in amount?

Crismon: I think it was relatively unimportant, Dr. Burch, because the penetration of ultraviolet light is rather small, and what you are measuring in nearly all circumstances is the thin layer near the surface.

Burch: Does the method measure concentration of fluorescein?

Crismon: Measure of concentration in a relatively thin layer. Is that the way you interpret your fluorescence data, Dr. Minard?

Minard: Yes. I am sorry I cannot give you actual depths of penetration. I judge that the depth of penetration of the activating ultraviolet is the limiting factor. Actual measurements, so far as I know, have not been made in tissues.

Fremont-Smith: Dilutions would play a role, wouldn't they? The reduction of the height and in the slope?

C[ris]mon: I would think so, yes, afterwards. I do not see how dilution could influence to this extent, the rate of [rem]ov[a]l.

Fremont-Smith: Oh, no, but you didn't mean that.

Bur[c]h: I meant the upstroke of the trace.

Fremont-Smith: I should think it would be bound to play perhaps quite an appreciable role.

Burch That would tend to indicate that the vessels are less permeable.

Crismon That has been the suggestion by other people who have used fluorescein (17) but it seems a little peculiar to think about a change of permeability in that direction in the face of an accumulating protein in the fluid. It seems unlikely that a small molecule like fluorescein would be retained.

Burch That is why I wonder if dilution was the reason for the two being different.

Crismon I am sorry we do not have measurements that would give us that answer If we knew exactly how much fluorescein was removed per minute by leakage into the upper part of the ear which also becomes edematous, it would give us some help in answering

Menard The same sort of thing is seen in burns, in that the initial fluorescence following a burn is a hyperfluorescence, and then, with subsequent fluorescein injections, the degree of fluorescence as compared with normal skin decreases progressively Here again we are not entirely sure to what extent the later hyperfluorescence is a result of restricted blood flow into the area, and to what extent the edema may act to filter out some of the activating ultraviolet and emitted fluorescence.

Sellers Are the time relationships similar to those after burns? Because the lymph flow from a burned limb starts to slow up as you know after about eight hours or so until after twenty four hours there is very little lymph flow

Menard We have not correlated our findings with lymph flow and we have not followed the rate of disappearance of fluorescence as far as Dr Crismon s experiments show here.

Sellers May I presuppose what you might be going to say? When does the lymph flow start to flow again from the injured part in the case of cold injury or does it keep flowing fast for the period of observation?

Crismon Our measurements suggest that it begins to flow very soon after six hours Some time between six and twenty four hours there is evidence of reduction

Fremont Smith Does the reduction in lymph flow in this and in the burns suggest that the mechanical stretching of the lymphatics is not the reason for increased flow but perhaps that increased flow is the reason for their being stretched where they are being dilated?

Burch I have not worked with lymph flow McMaster (18) in his studies on lymph flow and tissue pressure, found pooling to occur in dilated lymphatics. Injection into the skin of edematous patients with congestive heart failure of a very small quantity of dye resulted in almost an immediate appearance of the dye in the lymphatics of the thigh. Normally the dye would be limited to a few millimeters of the site of injection during that same length of time.

Fremont-Smith He injected it under pressure?

Burch Yes. He was of the opinion that with swelling there was distortion of the lymphatics due to pulling of tissues around the walls. That was McMaster's concept. I do not know whether it was definitely established as being true.

Fremont-Smith I have some difficulty with that one.

Crismon We have no more direct information than that. This evidence of decreasing blood flow through the tissues, from temperature measurements and from measurements with fluorescein, raises the question: Where should we mark the time of onset of ischemia in tissues? If ischemia is a factor in tissue destruction, where should we time its beginning. Should we consider it to begin as soon as stasis occurs in the true capillaries — that would be ten minutes after a part is thawed — or shall it be considered to start at fifty hours after injury when the last traces of blood flow have gone?

I do not have direct information about this but it would seem that when capillary flow is drastically restricted by stasis, the cells immediately in the environment of those closed-off vessels becomes asphyxiated and as far as those cells are concerned, their own ischemia begins early.

Talbott Anoxia?

Crismon Anoxia. Their own blood supply is gone, whereas other cells nearer the vessels that contain flowing blood are much better off provided that those blood vessels are of the type that will permit exchanges of an effective magnitude.

Horvath If the tissue requires less oxygen, would they become anoxic then?

Fremont-Smith You mean when it is cold?

Horvath Yes.

Crismon I am talking about the stage after thawing.

In attempting to arrive at a comparison between the effects of ischemia and the effects of cold injury this question of when to begin the period of ischemia becomes important. Consider the comparison of tourniquet application with cold injury. If you leave the tourniquet on an extremity for a period of time that includes the duration of freezing plus the total time taken for thawing, then you produce in an extremity that is not cooled a type of injury from which it recovers invariably. There is no evidence of lasting injury if complete ischemia by tourniquet is employed through that length of time, and even for much longer periods. In fact in order to produce gangrene of the toes and necrotic changes in muscle, we found it necessary to keep tourniquets on for three and a half to four hours when the limb is allowed to remain at 25° C. (19)

We were wondering about some of the metabolic changes that go on in tissues deprived of their blood supply. We analyzed skeletal muscle

taken from extremities injured by ischemia, and also by cold plus the inevitable ischemia that goes with it.

Figure 16 illustrates the accumulations of sodium and of water in

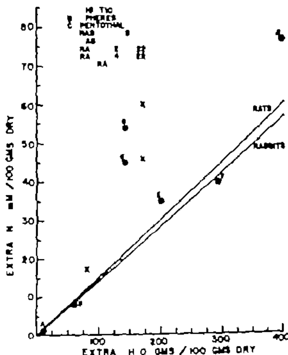


Figure 16. Accumulation of water and sodium in rabbit leg muscle after various forms of injury

muscles from rat and rabbit legs, in which various types of injury were produced. Some of them were injured by tourniquets applied for one hour (Group D). Some were injured for four hours and sampled at twenty-two hours. The rats in Group F had a tourniquet on for two hours and were sampled at twenty-two hours. The rats of Group G had tourniquets for four hours, and were sampled at twenty-two hours.

In addition to the groups mentioned, some had all of the major vessels ligated; others had the smaller arterioles blocked with microspheres (20, 21). These microspheres were injected intra-arterially and had a mean diameter of forty microns. We had occluded, in that experiment, a very large number of small vessels in contrast to the blood flow reduction accomplished either by tourniquet or by ligation of major vessels.

The crosses mark the sodium accumulations that were found in frost-bitten muscle. The technique of this examination compared the injured

muscle with the contralateral uninjured muscle of the same animal. The data are expressed as a plot of extra sodium against extra water on the Y and X axes respectively.

If muscles from injured and normal legs are analyzed and we subtract from the water content of injured legs the amount of water found per unit dry weight of muscle in the uninjured leg, then the difference is expressed as extra water. The same method is used to derive figures for extra Na.

Two diagonal lines are drawn to describe what we might expect if all of the accumulations of water and sodium consisted of added extracellular phase, that is, with sodium dissolved in the same concentration as that in the plasma. Thus, if the data fall on the diagonal line, the accumulation can be considered as an ordinary edema. If the values, however, are above it, then the sodium must have penetrated a water phase that was bigger than the water phase outside of cells. Whether the sodium has gone inside the cells or has in some way become excluded from the usual equilibrium we have no idea, but for purposes of our discussion it has been considered to represent cellular penetration of this ion, which is chiefly a denizen of the extracellular phase.

The severe injuries, including the four-hour tourniquet group, frostbite, ischemia produced by microsphere injection, and the injury produced by pentothal injected intra-arterially (22), are all associated with accumulations of sodium in excess of accumulations of water. Intracellular accumulation of Na is a nonspecific event that occurs after almost any sort of severe injury. It will occur in certain tissues even if the injury involves only the deprivation of substrate. It represents a metabolic defect. The tissues fail to resynthesize glycogen, for example; they fail to take in potassium from the extracellular phase. This metabolic failure has nothing specific to do with cold but is simply an expression of injury to the tissue.

In the case of frostbite and other forms of ischemic injury, these changes are detectable within twenty-four hours. In our experience the gross appearance of the muscle gave us no clue as to whether or not the injury was a reversible one. We could not distinguish by looking at the muscles grossly between the ones that had been occluded for one or two hours by a tourniquet and those that had been occluded for four hours, and yet the chemical pattern was quite different. We note from Dr Lewis's observations at Randolph Field that the microscopic appearance of muscle that has been subjected to cold injury is quite different from the normal appearance (23).

I should like to summarize, then, by saying we can demonstrate that cold of itself does not seem to account for the types of injuries seen after

frostbite, but some event concerned with the changes that take place *after thawing* does appear to be related to the injury

The tissues that survive cold injury must do so by having at least some surviving cells in injured tissue, and they must have some preserved blood supply I think we cannot exclude these facts in accounting for such phenomena as survival of frozen tissue, rapid warming, and survival of tissue after various other therapeutic measures, when the injuries are as severe as those used in our experiments namely exposure in liquid for three minutes to −55 C.

If any treatment is to be effective, I think that it must be applied very quickly and lies distinctly in the category of a first-aid measure. In support of Dr Shumacker s point, I say that nothing that we have been able to do to these animals in the later phases of their response to cold injury has been in the least effective.

Fremont Smith Have you been able to compare the pressure of blood flow in rapid warming to that in slow warming? In other words, do we know anything about the difference of the dynamics within the tissue in rapid warming as compared with slow warming?

Crismon We have interstitial fluid pressure measurements — a few of them — but no measurements of blood flow

Fremont Smith Would your impression be that rapid warming gives you a much better and quicker circulation through the injured part than slow warming does?

Crismon It gives it much sooner but more important than that, it persists You do not get these long tails on the first curves they come down much more promptly

Fremont Smith You do not go into secondary ischemia in the same way with the rapid warming that you do with the slow spontaneous warming?

Crismon I wouldn t put it that strongly If you look at the ear under the microscope, you find that you have not prevented the stasis in true capillaries by rapid warming It still occurs

Fremont Smith Does it occur just as much?

Crismon As far as I could tell, there was no difference, and the protein concentration of the edema fluid after rapid warming was just as high as it was without any treatment, so that we do not appear to have influenced that initial stage of vascular injury in the least.

Fremont Smith Is the edema loss greater?

Crismon It seems to be even greater and lasts a little longer if anything

Shumacker My associates and I have been very much interested in the relationship between edema and the ultimate result. We have found

no correlation between the degree of edema and the ultimate tissue damage, and I believe no one has been able to. I think Colonel Lewis's experiments are in agreement. I should like to illustrate the point by one specific experiment (Figure 17) (24). One closely clipped hind leg of each of

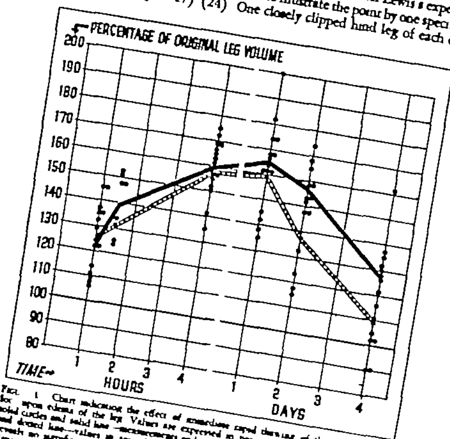


FIG. 1. Chart indicating the effect of immediate rapid thawing of the frozen rabbit foot upon edema of the leg. Values are expressed in percentage of original leg volume; solid circles and solid line—measurements and means, values in untreated controls; open circles and dotted line—values in animals treated by rapid thawing. Statistical analysis of data reveals no significant difference except for observations made on second and fourth days. Reprinted by permission from Shumacker, H. B., J. Surgery (in press).

sixteen rabbits was frozen by immersion up to the hock in an ether bath cooled to −20° C. with carbon dioxide for five minutes after solidification of the limb. The feet of eight rabbits were thawed rapidly by immediate immersion for two minutes in water at 4° C. The remainder were allowed to thaw spontaneously at room temperature (26° C.). The volume of each leg had been measured before injury by its displacement

of water from a graduated cylinder a method which gave reproducible results within ± 3 per cent. The volume of each leg was then measured periodically after freezing There was no significant difference in the rapidity of development or degree of edema reached in the two groups. In this experiment the edema subsided *more rapidly in the rapidly thawed* group Though edema developed with comparable rapidity and to the same extent in the two groups, the end results were quite different as far as tissue loss was concerned One animal in the control group developed no gangrene (14 3 per cent) and three in the rapidly thawed group (37 5 *per cent*) *did not*. Gangrene more extensive than involvement of toes developed in seven of the control group (87 5 per cent) and in only one of the treated group (14.5 per cent)

Lempke and I (25) were interested in making controlled observations concerning the effectiveness of the prolonged local application of cold to the frozen part By using a device by which the mouse could be kept in a snugly fitting cage with his tail in a glass tube projecting into a constant temperature bath (Figure 18) we were able to keep the previously

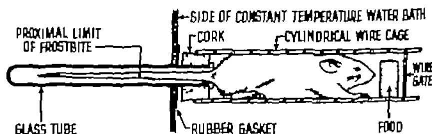


FIGURE 18. Diagrammatic representation of apparatus used for prolonged cooling of the frostbitten tail of the mouse Reprinted by permission from Lempke, R. E and Shumacker, H. B Jr *Yale J Biol & Med* 21 521 (1949)

frozen tail chilled for a long period of time. Actually we kept the water bath at a temperature of from 1 to 3 C., and kept the *tail exposed* to this water bath for seventy-two hours The results were considerably worse than in the untreated control group in which the frozen tail was allowed to thaw spontaneously at ordinary room temperature, and much worse than in the group treated by rapid thawing

Edholm I did not quite get the conditions What were you doing, cooling the tail?

Shumacker First we froze the tails of mice. In one group the frozen tail was then thawed rapidly by immediate immersion for two minutes in water at 42 C. Seventy-four per cent sustained no loss of tissue and in only 16 per cent was more than the *distal centimeter of* the tail lost. Another group was allowed to thaw at ordinary room temperature Only

5 per cent sustained no loss of tissue, and 73 per cent lost more than the distal centimeter Another group was placed immediately in the apparatus mentioned and kept there for seventy two hours with the water bath at 20 C. The damage was greater than in the control group There were none which survived without any loss of tissue, and 91 per cent had loss of more than the distal centimeter of the tail Immediately after freezing another group was similarly placed in the apparatus and kept there for seventy-two hours with the water bath maintained at from 1 to 3 C. These animals sustained even more extensive damage in all of them the gangrene caused loss of more than the distal centimeter of the tail If the results are analyzed according to the mean loss of tissue in centimeters of tail, the results are similar The four groups sustained respectively the following mean loss of tissue 0 39 1 76 2 32 3 7 cm.

Barch How long was the part in the bath and what was the temperature of the bath when the part froze?

Shumacker You wish to know what was the freezing injury?

Barch No what were the temperature and the time of exposure?

Shumacker The distal 6 cm. of the mouse s tail was frozen by immersing it in an ether bath cooled to − 15 C. with solid carbon dioxide snow The tail was left in the bath for five seconds after it had become solid fied.

Blair I should like to insert here one word of caution one should not try to compare recovery from edema in the tail of the rat with that of the ear or leg of the rabbit We have noticed in all our experiments that the ear or leg of the rabbit can have massive edema and still obtain total recovery without loss of any tissue whereas a much smaller degree of edema ppearing in the tail of the rat will usually produce gangrene and loss of the tail We may be wrong, but we think the answer to such an observation is probably this In the leg and ear of the rabbit massive edema can occur without disturbance of blood supply to the part but in the tail of the rat particularly near the base where the fur begin and the skin is very t ghtly ttached any swelling disrupts the bl od supply and produces ischemia Thus, t is merely a matter of d fference n anatomical structure of the two Often we think the loss of tissue t the rat s tail may be due to edema swelling and the esulting ischemia Such has been our observation, and we think one should use caution in trying to compare ecovery from edema in the ea or leg of the rabbit w h that from edema in the tail of the rat

Crismon I think that point is well taken. I should like to clarify our point of view on that bit We began with the assumption that edema might well have something to do w th the amount of injury and adopted two means of controlling edema after cold injury as therapeutic measures (6) One of these was the pplication of rigid casts of plastic material tightly against the foot or with padding The other was to allow edema

to occur and then to apply a padded pressure dressing We had enough encouragement by both of those methods to suggest that edema might well have been an important factor in destruction of tissue. It wasn t until we did the work of rapid warming and found that we could get recovery without influencing the edema at all that we came to the conclusion that edema per se was not the necessary single cause of gangrene.

Fremont Smith In the foot?

Crismon In the foot or in the ear

Fremont Smith But not in the tail.

Crismon We did not study the tail at all

Talbott The potentialities for constriction of the small vessels in the foot and the ear are similar

Crismon Our dilemma is this If edema is not a factor in destruction of tissue by gangrene after cold injury then why did we get benefit from closed plastic dressings and pressure dressings? We have no answer for that at all After our work was reported, I discovered that other people have applied those methods without very much success

Mowrey Clinically it has been observed that in the boys who have been wearing combat boots and who develop swelling, the sooner the boot is removed, the better your results are. Where there is edema and a combat boot is left on for a period of time, you get more damage than you do if the boot is removed early

Shumacker As soon as thawing had taken place and before any swelling had developed, we applied plaster boots to the previously frozen feet of mice, rats, and rabbits (27) Similar casts applied to normal extremities did no harm The end result of frostbite was not improved in any of these species even though the development of edema was effectively prevented Indeed, in the rat more extensive gangrene developed in the treated group than in the control group

Mowrey Have you used heparin in your mice?

Shumacker We have used heparin, but not in combination with plaster casts.

Burch Returning to Dr Fremont-Smith s remarks concerning tissue pressure when dealing with nondistensible skin like the tail, elevations in tissue pressure probably will interfere with blood flow The same is true of scleroderma. In a hand with scleroderma and contracting fibrous tissue, the tissue pressure may rise considerably which may impair blood flow This is readily seen when a man with scleroderma of the hands flexes his hands slightly and paling occurs over the knuckles due to squeezing of blood out of the vessels.

In studies done some time ago I injected one cc. of normal saline into various tissues of the body and observed the change in tissue pressure (28) The eyelid or the loose breast in the female results in little or no change in tissue pressure following the injection of a whole cc. of fluid

On the other hand, an injection of the same volume into the subcutaneous tissues over the anterior aspect of the tibia results in rapid rise in tissue pressure

Fremont Smith The greater the stretchability the less will edema interfere with the circulation, and vice versa

Burch That is correct.

Burton I should like to emphasize the danger of generalizing from rat-tail experiments or even from mouse leg experiments to the human, because the conclusion that edema plays very little role in the final outcome wouldn't agree at all with the very large clinical experience of Webster in Halifax, on immersion foot, in which he was able to cut down edema by packing his cases in ice and keeping them cold (29) My impression is that that was quite favorable Is that right, Dr Sellers?

Sellers Yes, it was. They were quite enthusiastic about it.

Burton They had a tremendous number of cases.

Shumacker I would take exception to the assumption that Webster's experiences demonstrated that the end result in immersion foot was significantly improved by the local use of cold It is very difficult to control observations carefully under conditions in which the outcome is as variable as it is in clinical immersion foot, in which it is well nigh impossible soon after the injury to predict whether gangrene will develop in any given case and if so how extensive it will be It is not so important that local cold makes the injured person more comfortable at the time or reduces the edema We are concerned with the question of its effect upon the ultimate result. We are all familiar with other edematous states, in cardiac failure, renal failure elephantiasis, tourniquet edema No matter how massive the edema in these conditions, necrosis of tissue does not develop

Talbott But are they preceded by cold damage? In this instance we have cold injury and then the formation of edema and I do not think that the clinical occurrence of dropsy is a counterpart at all of this problem

Fremont Smith That factor I think, is really important and also the factor in the cases that you reported, Dr Burton, that you are not only preventing edema, you are also keeping them cold if you pack them in ice.

Burton Lowering the metabolism

Fremont Smith Lowering the metabolism and perhaps doing things to the circulation and so forth Again it isn't a clear comparison Binding them with flexible bandage would perhaps have prevented the edema without changing the temperature but we do not have data on that. I think in all these things we cannot generalize nor should we discount them because they don't fit in with another situation.

Shumacker No but the literature for the past two hundred years is

filled with statements that the injured part should be kept cool and allowed to thaw only slowly As far as I can tell, these statements have never had any controlled observations as a basis. *It is an extremely important problem* and it must be settled We must know whether it is right or not, and the question cannot be settled simply by greater comfort of the individuals. It is too bad, but there are practically no controlled observations in man. Dr Loyal Davis s group that was sent to England during the last war to study high-altitude frostbite, unfortunately rather late, tried to make such observations Selecting one individual with frost bite involving both hands with apparently equal severity they treated one limb by local cold packs for forty-eight hours and the other by exposure to ordinary room temperature. They could only conclude that the limb kept cool did no better than the other and probably did worse. It developed larger vesicles, was more uncomfortable and was subsequently more sensitive to cold than the other Unfortunately they did not make additional observations of this sort

The study of Adams-Ray and Clemedson to which I have referred several times dealt almost exclusively with milder nonfreezing injuries, and the results of their study must not be given too broad significance. It is interesting, however that they concluded that those individuals in which the injured part was treated by application of snow did worse than those rapidly warmed. Vesicles developed in 70 per cent of the former and 45 per cent of the latter The length of treatment was eight days in the first group and four in the second

In some way this question will have to be answered definitely and I certainly would be among the first to admit that one cannot content himself with experiments such as Lempke and I did with the mouse s tail. Someday we shall have to obtain clear-cut observations upon *man*. We have tried to use long-continued chilling in the case of the mouse s foot, but we succeeded in keeping the foot chilled for only one hour The results were worse than in the control group You did similar experiments, keeping the rabbit s foot chilled for several hours without improving the outcome, Dr Crismon.

Crismon Yes.

Shumacker I recognize the lack of definitive proof of the correctness or error of the assumption, and I say we must settle the matter by controlled observations. We certainly cannot continue to accept as ideal a method of management simply because time after time in the literature it has been alleged to be good

Fremont Smith May I make a comment here? Dr Burton brought up experiments in which the limbs were packed in ice not to prove the value of cold, but to prove that keeping edema out was important. You objected to his data regarding edema because they would imply that cold

was beneficial, which you feel probably was not correct. I think this is an interesting example of counterdiscussion where the discussion isn't necessarily relevant to the point that the initial person is making. I agree with you entirely that what we really have to do is to set up some experiments, and I do not see why this is not a place for volunteer human experiments which can be done at least initially on the parts of the limbs where you are not going to lose fingers or toes. Those experiments would not be as good as experiments which would be more dangerous involving the tips of the fingers but at least one could make a beginning of chilling equal areas on the forearm or calf and of having one of them exposed to warmth and the other one kept cold, one of them exposed to pressure and the other one not exposed.

It seems to me that you could get volunteers to submit to limited areas of injury in the same way that we get volunteers to submit to burns. One would not get final answers but the kind of data which would make possible definitive experiments subsequently. I do not believe you are going to get an answer to this kind of situation, as far as the practical aspects of it are concerned, without human volunteer experiments along this kind of line.

Shumacker. Dr Lange and his associates (30) have done some experiments of the sort you mentioned. They have produced spot contact freezing injuries in human volunteers. They reported that keeping such a frozen area cool with an ice bag for twenty-four hours before administering heparin increased the resultant tissue necrosis as compared with that noted when the frozen area was kept exposed at room temperature for the same period before heparinization or was not treated at all. There are painfully few controlled observations upon man, but those we know of do tend to confirm the results of animal experimentation.

Fremont-Smith. That cold is not beneficial.

Shumacker. Not at all beneficial and perhaps harmful.

Kark. Don't you have a comparable situation in the whitlow? I mean, the kind of infectious injury of the terminal phalanx of the finger which follows a pinprick and which rapidly produces edema and necrosis of the bone. As far as I can remember from my anatomy days, which I have forgotten, there are bands in the pulp of the end of the finger which prevent the development of edema, but locally an abnormally high tissue pressure develops, cuts off the blood supply and bone necrosis follows.

Siple. When we consider the idea of rubbing snow on a frozen extremity, I believe this procedure may have caused more damage than it has done good; however, the concept of slow thawing in extensive freezing of limbs requires further considerations. I refer to a conversation with Dr K. Büttner of Germany in which he described experiments carried out in Germany. I do not know whether there were some of

Butner's own experiments or not. As I recall, the experiments had to do with placing tourniquets on a dog's leg for an extensive period of time and keeping the leg warm in a bath. From this local metabolism continued at a high rate and in the absence of normal oxygen supply by circulation, the results upon release of the tourniquets were disastrous. The dog died almost instantaneously, presumably of toxic poisoning and shock. On the other hand, when the dog's leg with the tourniquet on for an equal length of time was immersed in a cold bath that chilled the tissue so that the local metabolism fell to a very low level and required very little oxygen, the release of the tourniquet caused little if any reaction. The animal suffered no ill effects. Butner concluded that in frozen or deeply chilled tissue where circulation has been reduced, the distal end of such frozen limbs should never be rewarmed to the extent of creating a condition where metabolism will increase because of rise in temperature before the circulation has been fully restored from the body to the limb as a whole, thus insuring a prompt supply of oxygen.

Butner further offered another incident to prove his theory. This concerned a lovelorn nurse who attempted suicide in earnest. She took a dose of poison — enough, he said, to kill a horse. However, to make certain of her death she went out into the bitter cold of a local park to freeze to death. Butner colorfully put it, " It was found stiff and apparently lifeless the next morning." The body was taken to a cold morgue to await identification. Hours later an attendant was startled to note a feeble sign of life in her. A stomach pump revealed some of the poison still unabsorbed. She was warmed very gradually and brought back to normal life. Bütner explained that the cold and subsequent low metabolic rate had offset effects of the poison, which was absorbed so slowly that the amount consumed was not lethal.

From Bütner's story one would conclude that the key of rewarming is the sequence rather than either a rapid or slow rewarming rate. That is, it is essential to rewarm the areas between the coldest extremities and the body proper so that circulation is ready to enter the frozen areas as soon as they are thawed. If the frozen extremities are rewarmed so rapidly that metabolism increases before the circulation farther up is unblocked, anoxia will set in and may cause disaster or serious damage.

Fremont-Smith: If you increase the metabolic needs before the oxygen can be supplied, you may get into trouble; however, if you keep them down until the oxygen can be supplied, you may not.

Horvath: This was originally based on some Russian experiments which were later repeated by the Germans. About 1933 there was some work done by the Russians on this. Then there were vague reports during the war that the Russians were using this type of treatment for frostbite, although they were never confirmed very well because they were received secondhand.

Mowrey This topic brings up one of my pet ideas. Practically it will not work in most cases, but I think that experimentally it might be nice to try. We think rapid thawing is of definite value, and yet if we increase metabolism by rapid thawing we are likely to get more damage. It seems to me the ideal method would be the use of diathermy as mentioned before, diathermy applied to warm up deep tissues and to keep the skin temperature cold with snow until you start getting it warmed up.

Siple Or progress with the diathermy warming down the limb, after making certain first that the torso heat has been fully restored to a point that would call for increased blood circulation to the extremities.

Shumacker In this discussion I believe we may have all neglected to stress the fact that the data from animal experiments to which we have referred concern the momentary application of warmth to the still frozen part in order to bring about its rapid thawing not the application of warmth to a limb which has been chilled but not frozen. Of course, in this respect the experimental observations are not relevant to the problem of the nonfreezing injuries, immersion foot or trench foot, and vice versa. Furthermore, it is perhaps still an unsettled question whether benefit results from the transient application of moderate warmth to the already thawed limb in case of real frostbite. In my laboratory the results of such studies have been somewhat conflicting. I believe, Colonel Lewis, you have found that the application of warmth after thawing does result in some benefit. Is that correct?

Fremont Smith After spontaneous thawing?

Lewis If you remember in Washington I said delayed rewarming up to one hour is beneficial and the results in that experiment were significant at the 5 per cent level and, therefore, had five chances out of a hundred of being an accident. Dr Crismon said he had bad results. I said "Before I get out on a limb, I am going to go back and do that over." I did, and the results were the same. Now I am going back again and do it a third time. It would be nice if delayed rewarming proved beneficial. I am not convinced now in the face of my two findings, but I am going to keep at it.

Shumacker You may be interested to know Colonel Lewis, that we also repeated our original study and that on the second occasion transient warming of the already thawed part seemed to result in some benefit, whereas in the first experiments no benefit had been noted.

Sellers Isn't that just the opposite of what you said about Dr Webster's and Dr Johnson's treatment of immersion foot?

Shumacker What?

Sellers That delayed rewarming is dangerous and valueless.

Shumacker No. This was not an effort to keep the limb cool at all. We are speaking now about the momentary application of warmth after the frozen extremity has been allowed to thaw as rapidly as it will under

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ordinary environmental circumstances We simply deferred warming the limb until thawing had taken place.

Fremont Smith That does correspond to continued cooling, to keeping it cool. I mean, its temperature remains cool for a long period of time, whether you do it on purpose or not.

Talbott But cooling at a level above that which produces damage.

Sellers Webster didn t describe it as cooling, but I think he used the same term, delayed rewarming While the experiments were not controlled as well as they should be, there were great plans afoot in Halifax, as there were in other places, to carry out controlled series, but fortunately or unfortunately immersion foot stopped occurring at that point.

Blair Weren t Dr Webster s observations entirely on immersion foot?

Sellers Yes I think it is another problem.

Blair It is definitely another problem.

Sellers I am still wondering what was the severe objection to the treatment, however

Shumacker My objections are these. I do not believe it was proved that local chilling produced significantly improved ultimate results, since no control observations were made. Though the observations were made upon immersion foot, the results of such studies are ever so likely to be transferred to all the other related cold injuries. We have, I feel, similar confusion concerning the application of measures to cool the affected *extremity in various ischemic conditions.* Whenever local cooling is used in ischemic limbs, it is employed in the hope that benefit will result from the consequent lowering of metabolic tissue requirements. Of course, local cooling simultaneously reduces blood flow to the part as well. Under such circumstances only harm would result if the local circulation were reduced proportionately more than the metabolic requirements We know nothing about the proportionate decrease in these two factors, and we have no way of influencing the effect upon one and not upon the other I have had a rather large experience with all sorts of peripheral circulatory difficulties and, though I personally have never used local refrigeration except in preparation of an infected extremity for amputation, I have in quite a few cases seen the results of local cooling instituted by others. In my experience only harm has resulted from such measures, and I have yet to see anyone who has benefited from local cooling except as a measure for preparing for amputation. It should be mentioned, of course, that the use of local heat is harmful in all conditions in which the limb does not have the capacity to increase its circulation satisfactorily I have not had personal experience with the method Webster used in cases of immersion foot, but I do not believe his experience with immersion foot should help perpetuate the concept that in frostbite it is helpful to delay thawing and to keep the extremity cool.

Sellers I quite agree with that furthermore, the basis for the method has the obvious deficiency of not being a controlled experiment.

Behnke Except that the gist of the experience of the Germans is summarized again in this German aviation medical volume (31) by the simple statement that one cannot make strict rules about every detail and mode of treatment, particularly under battlefield conditions, but that it is important to follow the general rule *Rewarm the chilled body rapidly rewarm the frostbitten extremity slowly*

Now the Russian experience, as reported by Canadian observers (32) is to rewarm the extremities rapidly and a recent informal Swedish report is said to recommend "Rewarm the frostbitten part rapidly and then cool down again.

So we are faced with the cook s dilemma. We have been talking about therapy but since this Conference is dealing with fundamental questions, I should like to know more about the basic physiology What is the basis for a particular type of therapy and what are we trying to accomplish? Have blood-flow measurements been made and physiological and biochemical procedures carried out in conjunction with the various treatments to try to find out what constitute the underlying principles for rational therapy?

Barton I would like to point out that I do not like Dr Shumacker s interpretation of his findings on cold as indicating it can be of no benefit in any condition Immersion foot is a very difficult problem, not only because the tissues have not been frozen, but there is usually a much more extensive damage, a larger volume of tissue involved than in frostbite, and it may be that keeping the limb in ice is necessary and of benefit for other reasons than those concerned with the injured tissue. The problem is not merely what the procedure does on that limb, but how the edema in that limb may be affecting the body of the man, the whole man. I am thinking of the loss of protein, the loss of fluid, which may push him much faster into shock.

It may be for these reasons that it looked to Webster that keeping the limb cold was better, whereas we have been thinking up to now just about the effect on that damaged limb, rather than the effect upon the whole patient

Shumacker Animal studies (23) have shown that, effective as is the momentary application of warmth to the frozen extremity in order to make it thaw rapidly when such rapid thawing is followed by continued application of warmth of, say 40 C. for a long period of time, tissue damage may be increased. I think no one who has recommended rapid warming has suggested that warmth be used in any way except momentarily to return the frozen part to its normal state as quickly as possible.

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Blair It is definitely another problem.

Sellers I am still wondering what was the severe objection to the treatment, however

Shumacker My objections are these. I do not believe it was proved that local chilling produced significantly improved ultimate results, since no control observations were made Though the observations were made upon immersion foot, the results of such studies are ever so likely to be transferred to all the other related cold injuries We have, I feel, much confusion concerning the application of measures to cool the affected extremity in various ischemic conditions. Whenever local cooling is used in ischemic limbs, it is employed in the hope that benefit will result from the consequent lowering of metabolic tissue requirements. Of course, local cooling simultaneously reduces blood flow to the part as well Under such circumstances only harm would result if the local circulation were reduced proportionately more than the metabolic requirements We know nothing about the proportionate decrease in these two factors, and we have no way of influencing the effect upon one and not upon the other I have had a rather large experience with all sorts of peripheral circulatory difficulties and, though I personally have never used local refrigeration except in preparation of an infected extremity for amputation, I have in quite a few cases seen the results of local cooling measures by others In my experience only harm has resulted from such measures, and I have yet to see anyone who has benefited from local cooling except as a measure for preparing for amputation. It should be mentioned, of course, that the use of local heat is harmful in all conditions in which the limb does not have the capacity to increase its circulation satisfactorily I have not had personal experience with the method Webster used in cases of immersion foot, but I do not believe his experience with immersion foot should help perpetuate the concept that in frostbite it is helpful to delay thawing and to keep the extremity cool.

Sellers I quite agree with that furthermore, the basis for the method has the obvious deficiency of not being a controlled experiment.

Behnke Except that the gist of the experience of the Germans is summarized again in this German aviation medical volume (31) by the simple statement that one cannot make strict rules about every detail and mode of treatment, particularly under battlefield conditions, but that it is important to follow the general rule *Rewarm the chilled body rapidly rewarm the frostbitten extremity slowly*

Now the Russian experience, as reported by Canadian observers (32) is to rewarm the extremities rapidly and a recent informal Swedish report is said to recommend 'Rewarm the frostbitten part rapidly and then cool down again.

So we are faced with the cook s dilemma. We have been talking about therapy but since this Conference is dealing with fundamental questions, I should like to know more about the basic physiology What is the basis for a particular type of therapy and what are we trying to accomplish? Have blood-flow measurements been made and physiological and biochemical procedures carried out in conjunction with the various treatments to try to find out what constitute the underlying principles for rational therapy?

Barton I would like to point out that I do not like Dr Shumacker s interpretation of his findings on cold as indicating it can be of no benefit in any condition Immersion foot is a very difficult problem, not only because the tissues have not been frozen, but there is usually a much more extensive damage, a larger volume of tissue involved than in frostbite, and it may be that keeping the limb in ice is necessary and of benefit for other reasons than those concerned with the injured tissue The problem is not merely what the procedure does on that limb, but how the edema in that limb may be affecting the body of the man, the whole man I am thinking of the loss of protein, the loss of fluid which may push him much faster into shock.

It may be for these reasons that it looked to Webster that keeping the limb cold was better whereas we have been thinking up to now just about the effect on that damaged limb, rather than the effect upon the whole patient.

Shumacker Animal studies (25) have shown that, effective as is the momentary application of warmth to the frozen extremity in order to make it thaw rapidly when such rapid thawing is followed by continued application of warmth of say 40 C. for a long period of time, tissue damage may be increased. I think no one who has recommended rapid warming has suggested that warmth be used in any way except momentarily to return the frozen part to its normal state as quickly as possible.

Interestingly enough, Adams-Ray and Clemedson say that the Swedish

Army bans treatment with snow and recommends rapid warming of frost bitten limbs

Gottschalk Have there been experiments in which the part was made to rewarm rapidly by reflex vasodilatation of the cold injured part such as by the application of heat to other parts of the body or by vasodilators such as alcohol? You would think that in such manner you could increase the blood supply so that it stays abreast of the oxygen requirement of the injured part

Behnke This was one of the German practices. Some German sur geons (33) used vaccines, with apparent success, to increase circulation to the part. Their emphasis was to increase blood flow to the injured tissue while maintaining a low peripheral temperature By low temperature they referred to a temperature value of 10 C., I believe It is well to define this low level not conducive to injury because in some of the cooling experiments the temperature to which the tissues were exposed during treatment may have been injurious Thus 5 C. may be injurious, whereas 15 C. may not There is probably a critical temperature that must be defined

Siple Is that for the totally cooled body or frostbitten limbs?

Behnke The frostbitten limb I think that everyone is agreed that with reference to the body the core of the body it is necessary to rewarm as rapidly as possible

I should like to ask a question about rewarming Dr Shumacker in your experiments when you speak of rapid rewarming how long does it take?

Behnke Oh, it is momentary!

Shumacker It takes just a moment In these experiments we submerge the frozen part in warm water for exactly two minutes, as Dr Crismon had done We investigated the effectiveness of several temperatures, and we found that 42 C. was the best. This happens to be the temperature Ariev used in his original studies, and nearly all investigators since have used the same temperature A temperature as warm as 50 results in harm rather than benefit (34)

In answer to the other question regarding indirect efforts to produce local vasodilatation, I might say that quite a few studies of this sort have been carried out In some, general vasodilating agents such as tetra ethylammonium chloride have been used. In other sympathetic blocks or operative sympathectomy have been employed The results have not been constant In some no improvement has been noted in others moderate benefit has resulted. When such treatment ... ever the improvement was never as dramatic as ... results, how tained with rapid thaw ... can be ob-

Edholm If block ... rozen extrem ... part of the body to ... used or if ... on, ... d to another ... vasomotor

tone, the local vasodilatation is counteracted by the existing state of local cold. I would suggest that if a physiological method of rewarming is used, it will be ineffective because of the low temperature of the part concerned. If the temperature in the cold extremity is measured, it will stay cold even with a complete block of the vasomotor system.

Shumacker That is just what happened. These measures did not result in any constant appreciable shortening of the period of thawing

Burton This raises a question I wanted to ask Dr Crismon. I accept his evidence and evidence of others that there is a prolonged decrease of blood flow What evidence have we of how much the decrease is due to a neurogenic vasomotor factor and how much is purely mechanical, either by the tissue pressure constricting the vessels or by intravascular clotting, or whatever you like to call it? Do we have any evidence that there is a big vasomotor component in the decrease of the blood flow? Have you, for instance, seen what would happen in a sympathectomized ear of a rabbit whether it would have suffered the same decrease of blood flow after freezing?

Crismon Our experience includes chemical blocking of the constrictor mechanism in the ear by injecting procaine into the region of the stellate ganglion. Others have used sympathectomized animals. In our experience the injury was no less severe in the sympathectomized or blocked animal

Burton How about the blood-flow studies? Do you do them on the sympathectomized animals, and does blood flow decrease just the same?

Crismon Perhaps there is delay of stasis in true capillaries up to half or three-quarters of an hour, but sympathetic block did not abolish stasis

Burton I would suggest, then, there is not much of a sympathetic element in this decrease of blood flow It is probably only from these two mechanical forces.

Crismon None that we could discover

Burton I think that is a very important fundamental point how much of this decrease in blood flow that is apparently causing all the trouble is due to a sympathetic element.

Talbott Have you any observations of blood flow in the unaffected area of the extremity during injury and following injury? It would be helpful to know whether or not the blood flow is markedly altered in the nonaffected portions of the extremities.

Crismon We have observed that it is, Dr Talbott. Fluorescein accumulates in that portion of the ear just as it does in the injured portion. We could detect no difference in intensity or timing Tittel (35) I believe it was, several years ago made some direct observations of vessels not only in the uninjured portion of the rabbit ear, but also in the frostbitten part. He reported a local region of narrowing at the juncture of injured and uninjured tissue, which one could make out quite easily by transilluminating the ear If you look at that region under the microscope,

you find the column of blood moves through very briskly The vessels that you can see in the uninjured part of the ear look just as they looked prior to injury I haven t watched them during the state of freezing or during the onset of hyperemia.

Barton I should like to mention a factor which I think has been rather forgotten, and that is the effect of cold *per se* on the circulation. We found in the isolated perfused ear that between a temperature of 40 (both of the perfusion fluid and the ear) and 0 C., the resistance to flow increased two and one-half times and this is exactly related to the viscosity Therefore, in a cold limb a very big factor is that the resistance to flow will go up two or three times simply because the limb is cold and the blood has greater viscosity I think we rather tend to forget this purely physical factor which enters into the problem of circulation in frostbite. From that point of view warming the limb would improve the circulation for a purely physical reason. The factor is about three times between a warm limb and an ice-cold limb

Crismon There must be something different, however In this circumstance of cold injury from that encountered as a result of ischemia alone, because if a tourniquet is applied and left on for two hours the tissues that are rendered ischemic do not undergo gangrenous destruction. That is about the maximum interval that you could predict for the duration of ischemia in the initial phases of thawing after cold injury so we are not concerned with ischemia that occurs during the time of cold. If we are concerned with ischemia, it is the prolonged ischemia that occurs after gradual closing off of the circulation in the interval between twenty four and fifty-two hours, or something of that order

Talbott Was the viscosity determined on venous blood returning from the injured extremity?

Barton No it was not. This was an experiment done with Ringer s solution because we didn t want the complications of blood It was a physical experiment We found merely that the resistance to flow as one cooled down the ear went up two and one half times. This is exactly correlated with the change of viscosity of Ringer s solution with temperature.

Talbott But that temperature is of the returning blood The arterial blood temperature has not dropped to the same level as that of the returning venous blood.

Barton Yes In our experiment we made it simple by having both the perfusion fluid and the ear at the same temperature.

Talbott If there is a change in viscosity with cooling of the blood, that would lead to a decreased flow of returning venous blood If the arterial blood is being supplied to the involved areas at the same flow rate that might contribute to the formation of edema.

Barton Of course, on top of this in the actual case one would have another increase of viscosity apart from that due to the temperature increase namely the factor of the increase of blood over that of plasma, so that you have the double effect in frostbite of the cold increasing viscosity and the concentration of cells increasing it also.

Horvath Not only that, but the arterial blood temperature would be down quite a bit because it is being cooled quite markedly by whatever blood flow is coming up on the venous side As Barett showed originally and we confirmed later there is a marked effect on the arterial blood temperature by venous blood coming up from a colder area, so that you could have really quite a marked change in viscosity owing to both those factors a change in the actual temperature of the arterial inflow plus the hematologic changes. This might make the changes even greater than 3 5 or 10 per cent that you mentioned.

Barton It might be up to five times with the two factors.

Crismon I think that it is an important point to consider in the discussions concerning the difference between injuries seen in the field and those that have been produced in the laboratory Soldiers that are exposed to cold may have prolonged cutting down of their peripheral circulation, and the actual duration of effective ischemia in those individuals may well be beyond our usual time limits.

Horvath Did you ever take an animal and put a pressure cuff on the leg to make it ischemic, and then freeze it and after freezing, release the ischemia?

Crismon Dr Essex at the Mayo Foundation has done that. He uses that method routinely because the temperatures for exposure that he used (about −15 to −20 C.) did not produce frostbite uniformly in his experimental animals unless he occluded the circulation. He puts a tourniquet on and immerses the foot while it is ischemic, and thus gets uniform injury

Barton This should bring us to the point about intravascular clotting that I want to hear discussed. I should very much like to hear a discussion whether intravascular clotting occurs or not, and so on.

Talbott Before we have a protagonist speak, I shall ask Colonel Lewis to tell us about his experimental work.

Lewis We tried heparin, as I told you in Washington at the instigation of the Surgeon General, because of the reports we had been reading in the literature. We could not get any results from heparin therapy We repeated the experiments of persons who had advocated the use of heparin, using the same doses, but could not prolong the coagulation time of the blood to the extent that the original investigators had done We concluded that heparin was without value in the treatment of frostbite

The use of heparin is based on the theory that the necrosis from frost

bite is due to thrombosis of blood vessels. We were quite certain that theory was not correct. According to those who proposed the theory the thrombosis occurred about seventy-two hours after the injury so we did some histological studies on muscle and got various changes very early Within seventy-two hours your macrophages have carried away all the necrotic muscle, and you have replacement fibrosis, so we know that you get necrosis very much earlier In fact, you can see changes within fifteen minutes after cold injury

My ideas are different from most of those I have heard today so different that I hesitate to talk about them for fear of getting into trouble.

Talbott I do not think you will get into any more trouble than the rest of us.

Lewis We have frostbitten 2,700 rabbit legs, so I think I should be allowed to draw my own conclusions. There are two theories, you know in general, as to the cause of frostbite necrosis. One is that it is secondary to the vascular lesions, and you can name them all from edema down to thrombosis and the other is that it is a direct cold injury a true thermal injury Of course you can always straddle the fence and say it is half and half and you never get into an argument with anybody but it has also been my experience that you do not solve many problems One of the two must be much more important, and may be entirely important in this problem

We are of the opinion that most of the damage, if not all, is due primarily to cold injury — not ice formation, I believe, although I do not want to be too opinionated on that score. That idea, however is not new the early German pathologists Rischpler (36) and Uschinsky (37) as well as the English investigators Blackwood (38) and Sir Thomas Lewis (39) believe it is a direct cold injury Lewis and Blackwood would lead us to believe it is due to ice-formation crystals. I do not, because of the histological picture The pathogenesis and the pathology are identical with that of burns We produced the same picture by immersing the rabbit's leg in 52 C. water and as you know mammalian muscle coagulates at 47 We ran it up to 50 just to be sure We let the rabbits live, some for three days some for seven, and took sections. I should like to show you two of them I did not have time to make slides. These are colored pictures of the tibialis anterior of the leg One was produced by cold and the other by heat, and you cannot tell the difference. If you guess, you have a fifty fifty chance of being correct. There is absolutely no difference in the pathologic changes (Figures 19 20)

There are two types of muscle necrosis After muscle freezes, as far as I know there is nothing that will bring it back. We have had no luck with rapid rewarming, which is the only universally good treatment that I know of experimentally I flashed some of these muscles down (put them in −40 C. alcohol) and it took about a minute to get the superficial

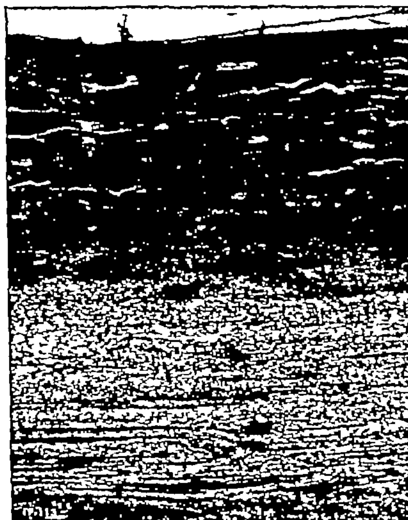


FIGURE 19 Leg immersed in −40° C alcohol until anterior surface of tibialis anterior reached 10° C (2 minutes, 45 seconds). Immediately warmed in 42° water. Survival time, 7 days. Section shows coagulation necrosis of superficial muscle layers and slow muscle-cell dissolution with fibrosis and exudation in the adjacent deeper layers.

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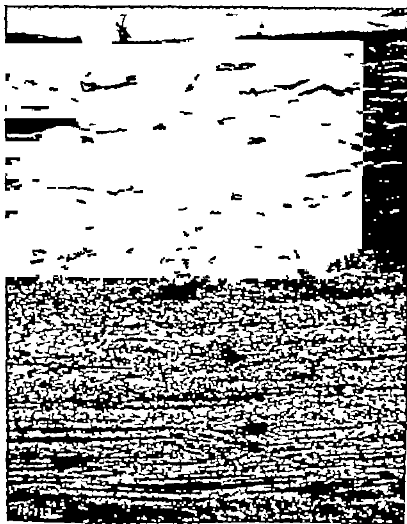


FIGURE 19. Leg immersed in −40 C alcohol until anterior surface of tibialis anterior reached 10 C (2 minutes, 45 seconds). Immediately warmed in 42 water. Survival time, 7 days. Section shows coagulation necrosis of superficial muscle layers and slow muscle-cell dissolution with fibrosis and exudation in the adjacent deeper layers.

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layers of the muscle right on the fascia down to −3 which is about the freezing point of muscle. Then we warmed it right away put it in 42 C water and within a minute or so it was back to body temperature, and we let the animal live for a week. You always get a coagulation necrosis of the surface layers of that muscle. If you flash it down to −2 C. instead of −3 C., you do not get coagulation necrosis, so I believe that muscle will stand freezing only and that it will not come back.

The second type is a slow wasting away of the muscle fibers with replacement by fibrous tissue. It occurs in the zone adjacent to but deeper than the coagulation necrosis. It therefore occurs at a slightly warmer temperature than the coagulation type.

Skin is something different. I am quite surprised today that there is as much resistance as there is to this rapid rewarming I do not know why that should be, except tradition. If you read the literature, you will see that it seems to be ingrained in people s minds to such an extent that we cannot change. But as far as skin is concerned, there can be no question that rapid rewarming is beneficial and skin is much more important than muscle anyway since 90 or 95 per cent of our frostbite involves the digits, and we do not have enough muscle there to worry about. But muscle makes a nice tissue for the purpose of studying the pathogenesis, because you do not have to be a pathologist to see these changes

As I say I am not so sure now about the delayed rewarming I do not think that the benefit of rapid rewarming is primarily due to shortening of exposure time to the cold It takes these legs about half an hour to thaw out in air, but the skin thaws out in a few minutes, so you really only shorten the exposure time of the skin from seconds to two or three minutes, so there is a question in my mind whether there isn t something more than just shortening the exposure time that has to be considered. There may be something else, some metabolic process that is altered. But the results are amazing.

I am not sure at what temperature the second type of necrosis occurs. I haven t got my sections out now That must occur either just about at the freezing point or at a point a little bit warmer perhaps in the slush formation but it is below the surface, and we know what the surface temperature is.

Now about these changes of the blood vascular system I do not think anyone can deny that we have astounding changes in the blood vascular system, but the joker is to hook these up with the necrotic process.

The common denominator in cold injuries is cold You injure the blood vessels and every other tissue, but when you have vessels under pressure that are injured, things happen which are immediately brought to your attention. To be sure, all tissues do not exhibit the same degree of susceptibility to cold injury

The question is Are we justified in attacking this vascular system in

BR 2

FIGURE 20 Leg immersed in 52 C water until anterior surface of tibialis anterior reached 50 C (3 minutes, 5 seconds) Survival time, 7 days. The pathologic changes are identical to those in the muscle exposed to cold.

cold injury? I am not sure It may have some influence, but I do not think it is very important, and if we are going to treat the vascular system in cold, we have got to start treating it in burns, because the pathogenesis and pathology of necrosis are identical in the two conditions.

Burton How about the physical chemistry of protein? Why should protein coagulate at −2 C.?

Lewis I do not know I have asked why it coagulates with heat. They tell me that something is altered in the molecule that what they call denaturization, an unfolding of the molecule, altered the solubility

Burton Do they know of a similar physiochemical process going on at −2 C.?

Lewis Not so far as I know the reason now When muscle freezes, it is gone so the only thing you can say about rapid rewarming is that it saves the thin zone of muscle in the borderline between freezing and non-freezing However after about four or five experiments, and waiting several weeks we got a significant improvement.

In all experiments, the improvement was in favor of the diathermy and the same holds true for warm water But you do not get the astounding results with muscle that you do with skin. There must be a critical cold that skin cannot stand, but I do not know right now just what that level is. I think it is about −15 C. for thirty minutes in an alcohol bath but for shorter exposure times the temperature would be lower

We have tried cortisone because it was forced on us. Someone took some over to Korea, I understand. We got negative results as far as the extent of tissue necrosis was concerned, with the doses we used. We thought we used an average dose. In a 2 5 kg rabbit we used 5 mg in divided doses twice daily the first two days, and then cut it down to three in divided doses of 1 5 mg for five days and killed them on the sixth day The per cent muscle necrosis was the same, and the skin in cubic centimeters was the same in the cortisone-treated and control animals

I should like to agree with Dr Shumacker about these clinical studies in frostbite *I do not think they are worth much. We have got to go back* to the laboratory and work on well-controlled animal experiments, because, as I said, you cannot tell by looking at a patient how severely he was injured by the cold and that goes for heat too I guess. We must have adequate controls. In order to study treatment in particular you might have such a small benefit it isn t measurable by our methods. Unless you have controls you never know whether you have an actual improvement or not You may think you get a worsening in your patients when in *reality you do not have a worsening but a beneficial treatment* I believe that most of the clinical reports that I have read are not sound so far as evaluating therapeutic measures are concerned

Some of the German articles in the volume of *Aviation Medicine* are not very good, and I am not entirely sold on the Russian papers. One important contribution that came from them was that rapid rewarming was beneficial. Then they make a mistake they want to rewarm at body temperature, 37° C., saying if you rewarm above body temperature you will have an increase in necrosis. We know from Shumacker s work that 42 C. is better than 37 C.

I received a letter from Dr Essex the other day He said I am very pessimistic about the treatment of local cold I think the only fruitful field is in the field of prophylaxis. After the frostbite has occurred, I do not think there is much we can do after the part is thawed I think in the end we are going to treat them as we do a burn.

Alward Mr Chairman, I should like to ask Colonel Lewis a theoretical question because I doubt if it could be tested experimentally The question is this If it were possible to re-establish normal circulation following freezing of an extremity in the manner you describe, is it your feeling that the degree of muscle injury and necrosis would be the same as that observed in your experiments?

Lewis Yes.

Alward Even though normal circulation was re-established?

Lewis That is the way I feel

Edholm Have you any information about tissues other than skin and muscle, such as tendon and cartilage?

Lewis Only about tendons, and in 2 700 frostbitten rabbits we have not seen the process of tendon except in a rare case when we have severe secondary infection. We generally can prevent infection with sulfamylon ointment, since pseudomonas aeruginosa is the chief infecting agent in our animals

We have kept our animals a week after exposure as a rule We have kept some animals four or five months for special reasons, so when the leg is gangrenous, sometimes you have secondary infection. But if necrosis is vascular in origin, why don t we get more necrosis of tendon, since tendons do not like to have their blood supply interfered with? The sequence of tissue susceptibility in the tissues that we have studied is as follows The most susceptible is muscle. Second is the connective tissue which supports the muscle. You can see in the picture at the top that everything is dead As you go down, only the muscle is dead There is connective tissue proliferating like wildfire. Third is the skin, and fourth is the tendon I do not know why the tendon hasn t become necrotic, but I suspect that it is particularly resistant.

Horvath I thought bone did become necrotic, and that there is later regeneration of the bone.

Lewis We haven t studied the bone. The tissues we studied were

the muscle connective tissue supporting muscle, skin, and tendon. We have not examined the bone. I am sure it will become necrotic. I am quite sure any tissue can be killed by cold — but some easier than others.

Kark You used cortisone in the animals, giving it only twice a day?

Lewis That is right.

Kark I wonder whether that is the correct way to use cortisone, since it has been shown that you get better results if you give it continuously over a long period of time, or at frequent intervals.

Lewis That is the way it was recommended. We took the average dose, and that is the way we gave it.

Kark I wonder what Dr Conn thinks about that.

Conn By what route was the cortisone given?

Lewis Intramuscularly twice a day

Conn It usually has had at least a twelve hour effect when given intramuscularly Twice a day is satisfactory for continuous activity

Behnke Colonel Lewis, if the measures to restore circulation are not of any avail what are you going to learn from a controlled animal experimentation? I mean, how do you explain the benefits of rapid rewarming? From your animal experiments it appears that the duration of exposure to cold, which is regarded as the prime injurious agent, is decreased by rapid rewarming The laboratory experiments are quite artificial compared with the cooling that may occur in the field. In the field the time factor is usually so prolonged, that is, with reference to exposure of tissues to cold, that the few minutes or half hour interval of rapid rewarming may be too short to be effective.

Lewis *I do not know that is something I cannot answer*

Behnke What procedure would you use for therapy of frostbite in human beings?

Lewis What would I do? I would rapidly rewarm it until it is thawed, and then I would put a sterile dressing on it.

Behnke Would you employ rapid rewarming to shorten the time of exposure?

Lewis That is one factor There may be something that is metabolic, I don t know I am quite certain it is not an increase in the blood supply for example. One reason that I feel this way is the similarity of the burn lesion. I am astounded at reproducing identical lesions, including the vascular changes, with heat.

Birch Don t you think, though, that the state of the vascular system will influence healing? After all, blood vessels must be injured too. This is probably true also of immersion foot, where the temperature does not drop to the level of freezing, as was encountered in people who fell into the sea. Of course, blood vessels are injured aren t they? All cells that are burned are injured.

Lewis All cells are injured by burn or cold. I didn t say they weren t.

Why not blame the necrosis on all these hemorrhages?

Barch The point is I am of the opinion that the state of the blood vessels must influence the pattern of healing even though it is not primarily responsible for the injury

Lewis I think they do.

Barch In treating burns, consideration in treatment should be given to the vascular system.

Lewis You cannot rebuild blood vessels

Barch That is the point, and if enough are destroyed by the primary injury healing must be altered accordingly Obviously if a blood vessel is burned in half, the tissues distally must suffer

Lewis When you burn a blood vessel in half the blood-vessel tissues distal to this must suffer You shouldn t work in a zone where you completely burn or completely freeze a tissue to death. You have got to work in the twilight zone if you are going to do your work. If you occlude a blood vessel by burning it, you are going to get necrosis, but you get injury of blood vessels in either one That is the only way you can explain it.

Barch But to say it is due to the blood vessel damage alone would be just as erroneous as to say the state of the vessels has nothing to do with the healing process.

Edholm You gave a definite temperature for the freezing point of muscle. Can you give any precise figures for skin, as you have been able to do for muscle?

Lewis As I told you, I am not sure When we determine skin necrosis we do it by measuring the square centimeters of the skin necrosis, and the temperature is at −15 C in alcohol for 30 minutes and we get extensive necrosis in almost 100 per cent of animals If you warm the temperature 3 C. to −12 C you get skin necrosis in about one fourth of the animals only

Edholm Minus 15 to −12 C would be the critical temperatures

Lewis Minus 12 would get muscle necrosis in 95 per cent of cases.

Gottschalk Are these animals anesthetized?

Lewis No We have had no trouble with that. Once in a while they will kick suddenly for no apparent reason, but I think the exposed legs become anesthetized very shortly and we do not have much struggling

Blair In evaluating therapeutic measures on experimental frostbite lesions, the majority of such lesions are pretty well delineated that is, the lesions are usually fourth-degree or third-degree to the line of immersion. You never see that type of lesion among the soldiers in Korea. The large or small toes are usually fourth-degree involved the adjacent area third-degree involved and second-degree or first-degree involvement further up the foot

Therapeutic measures that are carried out on patients with fourth-

degree slow freeze type of cold injury probably has no effect upon immersion-produced injury of exclusively fourth-degree severity However, in cold injury of gradual decreasing severity as seen in Korea, such treatment probably does influence *favorably the adjacent and less severely* injured areas, and may cut down the total tissue loss. A certain degree of cold injury appears to respond very favorably to specific therapeutic measures whereas more severe involvement does not appear to respond at all It is this latter type that is frequently seen in immersion-produced quick freeze injury

Lewis All animals do not develop necrosis You start at +5 C. for thirty minutes, and get sensory disturbance at +5 C. As you get down to −20 C you get complete loss of the leg, and in between you have all gradations of lesions Prenecrotic muscle change in the form of severe atrophy is the most astounding observation. The only article I have read that describes this atrophy of muscle in detail is one by one of the German pathologists Siegmund (31) The next most severe lesion is a slow fade-away necrosis and the next most severe injury is dead stop coagulation necrosis—the cells just die in their tracks. No *Colonel Blair I do not believe* that what you say is exactly correct. We do not work in a range where we injure the tissue up to the immersion line until it is gone. In fact, the slides that you saw showed that the only necrosis present was the central portion and anterior portion of the tibialis anterior That is where we took our section The rest of the leg tissues did not develop necrosis.

Blair I wondered if our cold injury treatment in Korea and Japan was doing any good at all until we visited the Prisoner of War Hospital in Korea and saw there North Korean and Chinese Communist soldiers who had *received no treatment for their cold injury* Enemy troops were losing up to twice as much tissue as our own soldiers from what appeared to be the same degree of freeze injury initially Part of our treatment was certainly preventing infection but something else was being done to prevent our soldiers from losing nearly as much tissue as the prisoners of war were losing from cold injury of similar degree

Shumacker Were they forced to walk?

Blair Probably Trauma, together with infection was most likely responsible for poor results among the prisoners of war

Birch Was their clothing poor?

Blair For the most part definitely not. But I was speaking only of the degree of initial freeze injury — that is, at the time of occurrence — being roughly of the same category It appeared that United Nations troops were getting better definitive treatment because they were not losing as much tissue It is probably true that much of the superior result was on a nontraumatic and noninfectious basis, but it still appeared that some specific treatment had beneficial effect in cutting down on total tissue loss

Lewis What treatment do you suggest?

Blair Antibiotics, but there are also many other things I do not L whether any of them are really specific for frostbite

Lewis I do not mean we shouldn t try to prevent infection. Certai give them penicillin and sulfa drugs nd everything else but that different from specific treatment for frostbite and I want to warn yo about saying that the Chinese Communists had the same degree of injury I believe, as Dr Shumacker does, that you haven t the slightest idea of the depth of the freeze

Blair The only thing you can do is to take it comparatively

Aloney I think the point Dr Burch made is a very valid criticism in using the Chinese as a control. However we do have a number of boys that we have seen who had probably more severe exposure than the Chinese did We can get a pretty good idea from those cases The Chinese had canvas shoes and sometimes socks on We had a number of boys who had exposure without any shoes or socks because the Chi nese took them away from them and they were marching through the snow in bare feet It may not be much different but at least the exposure is as severe. When you compare the two I think then you can begin to draw conclusions

I think another point could be well brought out concerning infection I believe you told me that the incidence of tetanus was quite high

Blair Not high.

Aloney About 37 cases out of 700 as against none that we had

Shumacker I should like to make some comments about Colonel Lewis s remarks. I have the greatest admiration for the work he has done. His discovery that the freezing injury which he inflicts upon the rabbit s hind limb results in such extensive and apparently irreparable muscle necrosis was surprising and I may say disheartening, to some of us It is a significant contribution Although I do not happen to be in agreement with him about the very small role played by the vascular element, I cannot help feeling that he is essentially right when he says the degree of damage resulting from freezing injuries is determined by the cold injury in its total effect on the one hand and the immediate treatment administered on the other

There are several reasons why I feel that the vascula element is more important than Colonel Lewis believes For one thing, necrosis of tissue does follow nonf eezing cold injuries in man For another it does seem reasonably well established that moderate benefit has appa ently re sulted from the use of certain measu es which presumably exert their effect upon the circulatory mechanism Though the esults are certainly far from dramatic, and fo that reason are perhaps open to some ques tion the use of rutin and antihistamines seems to have brought about improvement in the end results of experimental frostbite. Though there

is much disagreement, some experiments have shown apparent efficacy of heparin therapy. Similarly, though not all studies are in agreement, some have shown the autonomic blocking agents, general vasodilating agents, and local sympathetic block or sympathectomy to be of some value in reducing the incidence and degree of tissue necrosis. I would be the first to acknowledge that the benefit resulting from these measures tends to be trivial compared with the dramatic benefit of rapid thawing in the treatment of experimental frostbite, but they do tend to point to vascular alterations as being of some importance. I would also be the first to agree with Colonel Lewis that the animal studies up to the present time all suggest that the resultant tissue damage depends principally upon the seriousness of the freezing injury and whether or not the frozen part is thawed rapidly.

The question why rapid thawing is effective is an intriguing one, and I do not know the answer. Experiments with single-celled organisms demonstrate that the duration of the frozen state is comparatively unimportant. Spirochetes and malarial parasites, if properly frozen and thawed, for example, seem to survive as well if kept frozen for weeks as for days. Freezing of a portion of the mammalian body is, of course, quite a different matter, for all sorts of neurovascular interrelationships enter into the problem (40). At any rate, the resultant tissue damage is related to the duration of the frozen state in mammals, even though we cannot be sure that it is the duration of the frozen state per se which is important. One wonders then whether rapid thawing is effective merely because it reduces the length of the period during which the tissues are frozen. If one inflicts a freezing injury upon an experimental animal and notes carefully the time elapsing before thawing is complete, and then in other animals keeps the part frozen for a period of time equal to the freezing period and the period of thawing before terminating the exposure abruptly by rapid thawing, one finds that the latter animals tend to develop less necrosis of tissues than the former. Such observations suggest that rapid thawing does something more than simply shorten the period during which the tissues are frozen. What these additional effects are we do not know. There is something to suggest that the sudden restoration of a rather normal blood flow to the part may be of significance. As we have all pointed out previously, shortening of the period of thawing may inhibit the harmful growth of crystal size during the process and may tend to bring about a better physicochemical restitution of the frozen tissues.

Burch: Colonel Lewis, in your experiments with −15 C. for thirty minutes, did you observe 100 per cent incidence of skin necrosis?

Lewis: Ninety-eight per cent of animals develop some skin necrosis.

Burch: If you rapidly thawed the part, would that change the incidence?

Lewis Twenty-eight per cent, I think it was.

Birch That is a large difference.

Lewis That 98 per cent was the incidence the square centimeters I have forgotten — something like 290 square centimeters compared to 2 square centimeters of skin-area necrosis It is astounding

Horvath How do you account for the rather interesting sort of observation, made routinely in cold environments, that when you get local frostbite, relatively slow thawing (for instance, just by placing the hand, which may be fairly cool, over that area) also prevents necrosis?

Lewis That all depends on how severely it was frostbitten. I am sure you would get better results by putting something warm on it than by slow cooling. I do not see any indication for slow cooling any frostbitten tissue.

Horvath It seems to me that they both seem to be equally efficacious as to the end result obtained. Is that true?

Lewis You are talking about clinical cases again. You do not know how much injury a certain case had You have t have control animals, and you have to have treated animals. I do not know that anyone obtained bad results by rapid rewarming in experimental animals Lempke and Schumacker the Russians, Fuhrman and Crismon, ourselves — I think those are about all the reports that I know of — all report good results.

Horvath There have been some reports to the contrary too I was trying to reconcile this in my own mind.

Lewis Experimental work? I am not aware of them. If there are any I should like to read them.

Shumacker Early in my experience I stupidly overlooked the tremendous importance of wetness in hastening thawing Actually wetness is so important in facilitating the transfer of heat and cold to and away from the body that one may shorten the thawing time by immersing a frozen limb in ice water (40) The limb will thaw in a significantly shorter time than if left exposed in ordinary room temperature, and the end result will be improved somewhat Such extremities thaw even more rapidly however in warm water and derive much greater benefit.

Edholm Colonel Lewis, have you noticed any species difference at all?

Lewis We have only worked on the rabbit.

Edholm I wonder if by any chance the human muscle is in any way different.

Lewis I understand the muscles of the lady in Chicago were necrotic, that the upper levels might have been normal. I hope we get a full report on that case. It is very rare in human beings when you get f ostbite up that high.

Crismon Dr Rodbard said even the skin of her toes was normal in appearance at the time they had to amputate the legs

Lewis And the muscle was necrotic.

Crismon That is right.

Mowrey That is what they reported but it is not true in troops, because in human beings the dorsum of the foot or the entire foot will be covered with black eschar and some of that will peel off if it is superficial We haven t seen their muscles microscopically but functionally they have perfectly normal muscle left, and their function is perfectly normal

Lewis What muscle is there? The dorsum of the foot, you say?

Mowrey The dorsum of the foot and plantar surface.

Lewis I wonder if it were gone

Mowrey If it were gone, I do not think a man could walk on it.

Shumacker When we have a patient with necrosis of skin or superficial gangrene, with no deep gangrene, we can never be sure that the deeper structures were actually frozen.

Mowrey That is what I mean. That is why I say how do you get necrosis in deep tissue without getting it in the skin, too? I don t see why you don t get muscle necrosis as well as skin necrosis.

Lewis Because muscle will not stand cold as well as the skin

Edholm Isn t it a question of the actual temperature range that does occur? Do you ever get down to such low temperatures in muscle as are required to freeze it?

Lewis I think it is possible We had one case in Alaska a year ago that was frozen well up the leg Probably it does not occur very often, but I am sure it does occur The muscle is so highly specialized it cannot take the cold injury as the skin does. It is the purpose of the skin to protect the body I think it is reasonable to believe it is more resistant.

Minard In a discussion with Dr Crismon during the recess this morning, the possibility was suggested that tissue susceptibility to freezing might be related to water content Colonel Lewis has indicated an interesting relationship in tissue susceptibility to injury by freezing in pointing out that muscle is more susceptible than connective tissue, which in turn is more susceptible than skin, and that skin is more susceptible than tendon. I wonder if Dr Crismon would amplify the point he made in regard to the water content of tissues as a factor in susceptibility to injury by freezing?

Crismon I had reference there only to the total amount of intracellular phase material in the two tissues, muscle versus skin. Skin has only about ten per cent of its volume present in the intracellular phase. The rest of it is collagen fiber elastin, and other supporting material, whereas muscle has a much larger percentage of its total weight in the intracellular phase. It is in the intracellular compartment that metabolic activities go on and as we have seen from the work of Dr Meryman,

it is not impossible that the growth of large crystals outside the cells might deprive them of water initially only to permit them to take up that water osmotically during the melting stage and become destroyed. The amount of conspicuous destruction would be very large in a tissue like muscle, which is nearly all cellular material where it might be inconspicuous in skin where its large proportion is structural material. Only a few cells need survive in skin to restore it almost to normal afterwards. After all fibroblasts are quite capable of using framework material, as they usually do in a clot, in which to lay down their new collagen threads. We know new blood vessels can grow into masses of supporting tissue, and it is not impossible that the blood vessels, to the extent they participate in this injury, could be deprived of all of their living cells, and the larger ones could still carry blood because they retain their structure as tubes. These tubes may become relined with endothelium, and may even give rise to capillary beds.

It does not seem remarkable to me, therefore, that you find skin less easy to destroy than muscle.

Blair: Another possibility might be the type and duration of cold exposure. I have had the opportunity of observing Colonel Lewis's animals at the School of Aviation Medicine, and there is no doubt that in these animals the muscle is destroyed, while the skin, to all intents and purposes, appears normal. On the other hand I have also seen the cases of Colonel Mowrey in which there is gangrene and sloughing of skin and underlying tissues with apparently so far as we could see, no effect upon the muscle. The difference in the manner in which these lesions were produced may explain the discrepancy. The soldiers for the most part were exposed over long periods of time to cold, causing prolonged vasoconstriction which effectively cut down blood supply to the skin. Such prolonged disturbance of circulation doesn't occur in the few minutes of cold exposure in an immersion bath. It may be that other factors associated with prolonged exposure such as fatigue and exhaustion, may play a part in producing skin lesions and leaving muscles unaffected. I have never observed in our laboratory at Fort Knox where we have exposed rabbits and rats to dry cold over long periods of time, necrosis appearing first on any other location than the skin of the ear, tail, or feet. This would seem to confirm what appears to occur under combat conditions that is, after prolonged cold exposure as compared to very short exposures.

Edholm: What I was trying to get at in talking about environmental conditions is that the temperatures reached in the deep tissues on exposure to cold air will never be as low as that required to produce freezing. When the legs of animals are exposed to freezing mixtures of −15 C to −20 C, the deep-tissue temperature falls very rapidly as the limbs

are in a medium which is a good conductor of heat. On exposure to air, which is a very poor conductor the skin temperature will continue to fall, but the deep temperature will fall much more slowly and you may even maintain circulation through the deep tissues

Blair That was exactly the point I was trying to make. There are two entirely different conditions set up by immersion cold and prolonged exposure to dry cold You may have two different responses of the tissues, and that may explain why in one case you get muscle injury first and in the other skin injury first.

Fremont Smith Aren t we up against a perfectly characteristic dilemma where you have a clinical problem which you cannot reproduce exactly in the animal? Or to put it the other way where you can have perfect animal experiments, carefully controlled, but are not reproducing the condition which you are really primarily interested in, and that is, how to treat the patient The best animal experiments may not necessarily tell you the right treatment for the patient, no matter how carefully controlled they are for two reasons one, because there are species differences in many other respects, and until it is proved not to be so in this particular respect you have to have an open mind concerning species difference and secondly because the actual experiment on the animal is a different experiment than that on the human being therefore you have to say that the experiment on the animal has certain implications that do not necessarily carry over We have got to go through a series of tests. I am perfectly sure that some animal experiments done in the most ideal conditions would actually indicate the opposite of the best treatment of some clinical conditions which are superficially similar

I think one runs into this kind of dilemma again and again. You might even find that if someone did an experiment on a mouse and compared it with that done on a rat, he would get quite different results, whether he used an anesthesia or not.

Blair That is quite true, sir However if in producing experimental cold injury animals are subjected to identical conditions, degree, and duration of cold exposure to those experienced by troops in Korea, then a lesion is obtained which appears identical to that experienced by the soldiers. Variation from such technique produces lesions that no longer appear identical. I am speaking from experience with rabbits, but such an observation is probably true for other animals as well

Fremont Smith But your response to treatment might not be identical with the different species.

Blair That is quite possible.

Kark The woman at Michael Reese suffered a different type of exposure from those in Korea. I do not know anything about the length of time the men in Korea are exposed, but she apparently was out drink

ing, was lightly clad with just some nylon stockings on her legs, disappeared about midnight, and was found lying unconscious in a gutter about 4:00 A.M. I think that is the story. She had dilated peripheral vessels, since she had been drinking. There you are getting a very quick freeze, at a very, very low temperature, without any protective clothing at all and a rapid loss of body heat. That may be quite a different story to what happens in Korea. What is the time interval with most of the soldiers?

Blair: I talked with Dr. Rodbard several months ago in Cleveland, and found the exposure of the Stevens woman in Chicago to be approximately four hours at about −12° F. She was lightly clad and completely inebriated at the time. The soldiers in Korea were usually but not always, well clothed, and had had very little, if any, alcohol. Their exposure time was more often a matter of days rather than of hours. It was usually accompanied by fatigue, psychological stress, and occasionally inadequate caloric intake. So even here there is a very striking difference in etiological factors.

Barton: She had generalized hypothermia, too.

Blair: Very marked, down below 70° F., whereas in Korea the soldiers rarely have any hypothermia at all when reporting with cold injury.

Fremont-Smith: Are the boys in Korea stationary during such period, or perhaps walking and using their muscles during the period of chill?

Blair: Most often they had just completed a long march and were quite fatigued. Then they became immobilized and "pinned down" by enemy fire. Under such conditions they were unable to carry out even the basic principles of cold-injury-prevention training, such as changing socks, drying footwear, exercising and massaging feet. It was usually under such a state of total inactivity that the freeze injury occurred. It may or may not have been associated with breaking through ice and wetting feet, which was a very common occurrence.

Mowrey: One lieutenant was engaged in taking back some wounded in a truck. The truck convoy was ambushed, and he became unconscious from a shell. It was early in the morning when that happened. He awoke that night some time—he didn't know when, for it was dark. He had no boots on—the Chinese had taken his boots off—and his feet were frozen fast in a snowbank. Finally he broke them loose. He crawled during the rest of that night, and finally, just at dawn the next morning, got out to the Chosin Reservoir and crawled for four or five hours on his hands and knees across the ice, with the Chinese shooting at him before he got to the American lines. The temperature during that time was 30° below zero Fahrenheit.

Shumacker: What injury did he sustain?

Mowrey: Bilateral gangrene both of feet and of hands. That of his

hands was superficial. He ended up losing two or three digits on one hand and one digit on the other that is the distal phalanx only and he lost the toes of both feet.

Shumacker There was no muscle necrosis at all?

Mowrey Not that we could find

Shumacker I mentioned earlier that I could see no essential difference between high-altitude frostbite and the more common ground-type frost bite Although my experience with the former was not great, I failed to note any difference between this condition and ordinary frostbite

This winter I had the opportunity to treat a twelve-year-old girl from Arkansas who had gone barefoot to an outside privy in a temperature of about −15 F Her total exposure was very brief and probably did not exceed fifteen or twenty minutes. None of us could see any difference in the frostbite which she sustained and that sustained by other individuals under treatment at the same time who had incurred an injury over the course of one or more days There appeared to be no difference in the type of gangrene nor in the vasomotor alterations.

Blair What was the status of the skin and muscle?

Shumacker We noted no muscle necrosis, but then she had only superficial skin-deep gangrene as far as we could tell.

Talbott Certainly as one sees the patients on the wards it is difficult to distinguish frostbite from injury incurred over a period of only a few hours from that which took place over a longer period. As in many clinical problems, each patient is different from the next one, but there is a great deal of similarity in the two- three- four and five week periods of convalescence without appreciable difference as to whether or not the injury was contracted rapidly or slowly Is not that right, Colonel Mowrey?

Mowrey Correct

Fremont Smith Doesn t the four-day mean the frostbite took place in the last three hours of the four days?

Talbott No The officer was unconscious for at least twelve hours before he got into trouble

Fremont Smith But the frostbite might have taken place while he was climbing on the ice

Talbott No his feet were frozen in an ice bank.

Mowrey The temperature was 30 below

Shumacker One cannot ignore the point which Colonel Lewis tried to make, that any resultant fibrosis of digital muscles might tend to be overlooked since most of the finger movements are motivated by muscle masses situated proximally to the digits themselves. Occasionally in frost bite one must do a definitive amputation not through the line of demarcation, but proximal to it in order to get the best functional result. In such

circumstances it would be important to examine microscopically the muscle proximal to the line of demarcation. It would be most important to find out whether here, as in Colonel Lewis's experiments, one had muscle necrosis in an area in which the overlying skin was intact.

Fremont Smith Some men who are recovering from severe frostbite may die from some other simultaneous wound or injury and I should think there would be a considerable number of autopsies on such cases where this kind of study could be made quite extensively

Talbott That is not correct During the time that we were stationed at the Osaka Army Hospital, I do not recall a single death among four hundred cold-injury cases Did you have any deaths in your frostb te cases, Colonel Mowrey?

Mowrey None.

Fremont Smith If a man has a fractured skull and frostbite there is nothing in the frostbite that prevents him from dying of his fractured skull.

Mowrey We have had a number of those, and they have not died.

Fremont Smith Nevertheless I think the time will come, if the war continues, and if the pathologists and clinicians are alert to this particular problem, that when patients die of some other injury and are in the process of a healing frostbite, we can examine the muscles carefully

Mowrey There was one case in which amputation was done that might help I do not know what the studies are going to be at the Armed Forces Institute of Pathology on it Our pathologist said he could detect no change in muscle up to the line of demarcation, that there was an intimal proliferation of blood vessels for about a centimeter before he came to the line of demarcation At the line of demarcation there was complete thrombosis of blood vessels and necrosis of all tissue

Fremont Smith About how long after the injury was that?

Mowrey About six weeks

Crismon May I interpose a comment here regarding the problem of ischemia? In studies on animals in which ischemia was produced with tourniquet for four hours, gangrene was confined to the toes, but the muscles had undergone replacement by fibrous connective tissue. That was dissimilar sort of response in tissues that were equally deprived of blood. We became somewhat curious as to where the fluid goes in tissues that become gangrenous It became quite apparent that it was not taken up in the blood stream. Most of it escapes thro gh the surface, and it is the surface drying that is responsible for the appearance of gangrenous skin The muscle had no opportunity to dry out it was covered by skin I do not think anybody knows what would happen to muscle if it were exposed it might come to look just like skin, dry dark, and mummified

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Talbott That is not correct. During the time that we were stationed at the Osaka Army Hospital, I do not recall a single death among four hundred cold-injury cases Did you have any deaths in your frostbite cases, Colonel Mowrey?

Mowrey None.

Fremont Smith If a man has a fractured skull and frostbite there is nothing in the frostbite that prevents him from dying of his fractured skull.

Mowrey We have had a number of those, and they have not died.

Fremont Smith Nevertheless I think the time will come if the war continues, and if the pathologists and clinicians are alert to this particular problem, that when patients die of some other injury and are in the process of a healing frostbite we can examine the muscles carefully

Mowrey There was one case in which amputation was done that might help I do not know what the studies are going to be at the Armed Forces Institute of Pathology on it Our pathologist said he could detect no change in muscle up to the line of demarcation, that there was an intimal proliferation of blood vessels for about a centimeter before he came to the line of demarcation. At the line of demarcation there was complete thrombosis of blood vessels and necrosis of all tissue

Fremont Smith About how long after the injury was that?

Mowrey About six weeks

Crismon May I interpose a comment here regarding the problem of ischemia? In studies on animals in which ischemia was produced with tourniquet for four ho rs, gangrene was confined to the toes, but the muscles had undergone replacement by fibrous connective tissue. That was a dissimilar sort of response in tissues that were equally deprived of blood We became somewhat curious as to where the fluid goes in tissues that become gangrenous It became quite apparent that it was not taken up in the blood stream. Most of it escapes through the surface, and it is the surface drying that is responsible for the appearance of gangrenous skin. The muscle had no opportunity to dry out it was covered by skin. I do not think anybody knows what would happen to muscle if t were exposed it might come to look just like skin, dry dark, and mummified.

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HOMEOKINESIS

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RATHER THAN USE the term homeostasis I prefer to speak of "homeokinesis a word which seems more appropriate and more exact. Homeokinesis I would define as the processes and mechanisms through which the body attempts to maintain a condition of relative constancy at an optimum level for the most efficient functioning under the state of affairs existing at the time The effective operation of these homeokinetic operations can, and usually does result in a state of relative constancy i.e. homeostasis The problem of homeokinesis, as far as the relationship to cold is concerned is somewhat complex. Very few people have given it a great deal of thought from the standpoint of providing experimental evidence When I tried to find out some of the problems of regulation of the internal environment as far as local or minor cold injuries are concerned, I was disturbed to find that there was very little that I could report. Actually there is primarily one bit of evidence, which is somewhat contradictory in itself namely that some individuals, following a local cold injury may develop at a later date, a minor elevation of body temperature which may persist for some time This indicates that there actually may be some alterations in the homeokinetic state, and that we really ought to look more closely at this problem of what a local small area of damage may do to the entire body's regulation But there has not been any great interest in that sort of problem, primarily because everyone has focused his attention upon the local site of damage, and has tried to explain that. Consequently no one has been able to give us adequate information on what may happen to the organism generally

I have envisaged the problem of homeokinesis, as far as regulation of the internal economy is concerned in this way Here we are faced, in so far as generalized cold exposure is concerned, with the problem of the manner in which the body can adjust itself to meet a situation in which, although it has an external core that is cooled and an internal core that is still warm, it must nevertheless be able to respond at the time when the external core is heated and the internal core may have to be cooled, and then, finally where there is balancing of both areas.

Using that as a basis for the problem of homeokinesis, I thought I would start out with some ideas about temperature regulation, and point out how it is possible, just from evaluating the problem of temperature regulation, to bring in many of these problems of homeokinesis.

The first point has to do with the problem of metabolism, which is, of course, related to the problem of temperature regulation, because of the extra heat that is produced either to maintain or to prevent the fall in body temperature. There are these two possible methods by which this change in metabolism may occur One of the simplest, and the one with which most of us are familiar is the problem of muscular activity whether it is related to the simpler type of activity namely pilomotor activity extending into shivering, or whether it is absolutely gross muscular activity There is another aspect of temperature regulation and metabolism, and it has to do with the chemical factors concerned with raising the metabolism of the individual to meet the demands of his falling temperature.

Both of those are rather ticklish problems, because the evidence is as favorable for one of them as it is for the other

This is primarily an expression of regulation in terms of the endocrine system and the posterior hypothalamus The endocrine glands which have been implicated, and which may possibly have some effect upon this temperature regulation through increases in metabolism, have been many and varied the adrenals, both the cortex and the medullary portion the thyroid, which unfortunately probably responds somewhat too slowly to be of any great importance, or even to participate in the initial response to the falling body temperature. The adrenal cortex, which has already been shown to play a large role may have an even greater role in view of some of the newer work which is being done on the relationship of the cortex and cortisone compounds The anterior pituitary which, of course, has also been involved in the problem of homeokinesis, may be of utmost importance as the mediator organ. The epinephrine from the medullary portion of the adrenal gland is apparently of interest only in situations where the adrenal medulla may be absent or exhibit impaired function. Some evidence which has been collected indicates that the calorigenic action of epinephrine may not be much greater than that which is produced normally as a consequence of active muscular work (that is, shivering, and so forth) in the cold environment, so that it may not be able to increase metabolism to any great extent This problem requires more attention

The posterior hypothalamus may well be associated with the induction of shivering as a response to cold. However in view of the distressing character and inefficient caloric production of the shivering process, I should not like to consider this as an important function of the posterior hypothalamus in homeokinesis

Some of the most striking experiments concerning this may be those of Hicks and co-workers on the Australian aborigine, indicating some very interesting things as far as their ability to stand an environmental temperature of around 0 C. without apparent shivering Unfortuna

there is no evidence as to whether these individuals have an increase in muscular tensing, muscular tone, or whatever the term may be that you wish to use More work on this particular type of individual (cold-adapted?) might throw some light on the role of the muscle-tonus factor in the regulation of body temperature, in cold and in relationship to homeokinesis.

Another aspect of the temperature regulation concerns vasoconstriction. There are two possible ways in which vasoconstriction can influence the temperature regulation The first is that it results in a decrease in the thermal conductivity of the tissues. I shall say more about that a little later And then, of course, it aids in reducing the amount of thermal loss from poorly vascularized tissues.

The only thing that worries me about the role that vasoconstriction may play in the problem of temperature regulation — this part of the homeokinetic reactions — is that in general the range at which you can shift from complete vasoconstriction to complete vasodilatation is quite narrow Actually you can show an almost complete shift with an environmental temperature change from around 26° to around 31 C. Here you go from nearly complete vasoconstriction to almost complete vasodilatation.

Involved in the problem of vasoconstriction is the hunting reflex, which was discussed earlier this afternoon. Whether that is still a phenomenon which is related to the axon reflex, or whether it is one which has to do with the local reaction of the cells of the vessels, either the muscle cells of the arterioles or even the endothelial cells of the capillary has not, so far as I know been clarified. More important, is it of value to the organism or is it an indication of impending disaster?

One factor in vasoconstriction which has been lost sight of I think, until recently — and that came about primarily through the work that Dr Barett had done — is the relationship of blood temperature and its influences upon the responses of the body to lowered environmental temperatures. It is also possible, from some of the postulates that Dr Barett made, to relate this to local neural stimulation, and that to its relationship to shivering and to vasoconstriction.

It is interesting in this respect to consider what happened in several old experiments which may have been forgotten, one a rather interesting experiment on the exposure of man to cold water by I think, Lindhart I can t remember the name exactly now He noted an extraordinary difference in the response of the individual to his environment, that is, it made a difference whether or not the individual had been placed in a bath of carbonated water or in one of just plain water The carbonated water induced a great difference as far as the individual was concerned, in his response to the thermal stress and so forth he seemed to be much

more comfortable than he would have been if he had just been placed, at a prior time, in ordinary water

Fremont-Smith That is in cold stress, not hot?

Horvath This is in cold stress, yes.

It is also interesting that a somewhat similar thing can be observed by taking a man and shifting him from a bath of, say 15 C. to one of 16° C. The difference of one degree or two degrees is enough to make a great deal of difference in his responsiveness to the cold environment.

Fremont Smith Are you going to discuss the matter of carbonated water further? If you are not, I want to make a comment on it.

Horvath No I am just throwing these out as possibilities to discuss. I thought that perhaps someone else would want to talk about it. Go right ahead, Dr. Fremont Smith.

Fremont Smith I was just going to say that for an individual who is in a carbonated bath with walls around it, since CO_2 is heavier than air there will be an accumulation of CO_2 in the gas or the air immediately above the water and the individual will be rebreathing CO_2. As I pointed out to you earlier today in being exposed to cold there is hyperventilation, and certainly to hyperventilate when you are rebreathing CO_2 is very much more comfortable than to ventilate without rebreathing CO_2, as some of the people who have been subjected to high altitudes have found. That is possibly one of the reasons why it was more comfortable to be exposed to the carbonated water

Horvath The only difficulty with that is that they had the individual breathing through a tube at a distance.

Barton Dr Horvath, Magnus verified this (1) I think it was Magnus and Liljestrand. It is a very interesting thing, and it is true. A bath at about 33 4 C. feels neutral. But if you saturate the water with CO_2, a bath around 31 C. which feels very cold indeed if it hasn t the CO_2, feels neutral.

Fremont Smith So it is actually an effect on the skin.

Barton Some effect on the temperature sense organs.

Fremont Smith On the skin.

Barton Yes.

Horvath Which probably is related to this business of vasoconstriction. I am not sure that it is, but at least it seems to be related to it, and it might well prove an interesting point as far as generalizing man s responses to cold.

Crismon Doesn t it cause a vasodilatation?

Barton Yes, it causes a vasodilatation.

Dr. Bazett had a theory on the operation of the temperature receptors based on the gradient of temperature, which produced a pH change be-

tween the inside and outside of the cell (2) Therefore, you could argue that a CO change would do the same thing

Horvath Well, shifting an individual into a plain water bath which is just one or two degrees higher in its temperature does exactly the same thing as far as the local response is concerned

Burton Yes.

Burch What about results with the gas alone?

Burton We did not try the gas without water but Goldschmidt has shown that the gas is absorbed through the skin, so I think it would be the same thing

Horvath What do you say Captain?

Behnke Then, too, there may be a mechanical effect. There is an insulation.

Fremont Smith The bubbles are on the surface of the skin?

Behnke Yes

Burton There were no bubbles. It was just bath water saturated with CO_2 in solution.

Behnke Well, a lot of CO_2 is moving through the skin. There is no question about that

Burton Yes.

Behnke What effect that has —

Burton It produced a marked vasodilatation at once.

Behnke That would make one feel colder wouldn t it?

Fremont Smith No it would make one feel warmer in the skin, although one s temperature might fall faster

Horvath Yes, one s temperature does fall faster

Behnke Does the temperature fall faster?

Horvath Yes.

Burton A bath full of CO feels neutral even though it is at 32 C. In such a bath you lose temperature rapidly although it would feel fine at first.

Behnke It would be very interesting to measure the CO_2, the respiratory quotient, because certainly helium in contact with the skin comes into equilibrium so rapidly with the absorbed helium in cutaneous vessels that one can measure peripheral circulation.

Horvath That has been done by McClellan at Saratoga Springs I think it was Saratoga Springs. It was at one of the spas over here. He found there was something to it

Fremont Smith McClellan?

Horvath Yes

Fremont Smith Isn t it true that the question of whether you feel hot or cold depends upon the temperature of your skin? And if you have got a vasodilatation, you have got warm blood being brought to your skin, and hence your skin will actually be warmer in the CO_2 bath.

Burton This is a very well-stirred bathtub in which you force the skin temperature to remain the same

Fremont Smith Even beneath the surface

Burton Well, beneath the surface.

Fremont Smith Where the endings are O.K., I won t persist

Burton It is a question of interpretation.

Horvath Yes, it depends upon how far below the surface you want to go

Mowrey This aerolater that breaks up the spray of water and gives a bubbly appearance — wouldn t that do the same thing?

Horvath I don t know it

Mowrey It is a gadget that breaks up the spray of water and gives a bubbly appearance There is no CO present I know in the shower that we happen to have It is not as cold in that as it would otherwise be.

Horvath We have been doing some experiments with an agitator of the same type. It is just a motor a sort of turbine underneath the water which puts out a fine stream of air and disturbs the water considerably I can assure you that it makes you feel much colder at, say 16 than you feel if the water is not being agitated.

Fremont Smith You wish they would turn it off

Horvath Yes, you are hoping something will happen to it so that it will be turned off

Kark Are you losing much more heat that way or how much heat are you losing?

Horvath Quite a bit more For the length of time we were in, which was about twenty minutes we were losing about twenty five to thirty calories, which is a fair amount

Kark A useful thing for treating heat injury eh?

Horvath Another aspect of homeokinesis would have to do with the shifts in water which probably also are related partially to vasoconstriction, and therefore probably would be related to the temperature regulation.

One of the aspects is the change in blood volume It has been pretty well substantiated that there is a reduction in blood volume with an increase of fluid in the tissues, primarily in the intracellular phase That has been shown in all sorts of animals, starting off with the rat, and similar work has been done on the dog I am not too sure what this may do although it may have something to do with the thermal conductivity of the tissue that is, it may change the thermal conductivity of the tissue sufficiently to alter the sensory responses as far as temperature is concerned, and therefore the subjective evaluation of the individual as to the rate at which he is losing body heat

Fremont Smith That is, exposure to a cold bath will cause a drop in blood volume? I just want to be sure I understood correctly

Horvath Also to cold air

Fremont Smith Also to cold air?

Horvath Yes. A decrease in blood volume with an apparent shift of that fluid into the extracellular fluid first and then into the intracellular. Barbour originally showed this in rats, I believe, and since then it has been shown by several other individuals in other animals. It may alter the thermal conductivity

You know more about thermal conductivity Dr Burton.

Burton We had some evidence, but it does not alter the thermal conductivity greatly I think the blood volume change is more related to the economy of the animal and to the fact that to keep a complete vasoconstriction in the cold you have to put the blood, which was in the periphery somewhere You have to have a splanchnic dilatation, whereas when you have got rid of the excess blood volume vasoconstriction can be maintained without that compensation. So the body is, I suppose, under less stress when the blood volume has been reduced a little.

Edholm What are the time relationships in this blood volume change?

Horvath In cold air it is apparently a matter of approximately the first twenty four hours In water it seems to be a little more rapid than that — several hours.

Edholm Do you think this blood volume change is entirely explained by hemoconcentration, or do you think there is a reduction in the number of cells as well?

Fremont Smith I could not hear the last part of your question.

Edholm I wondered whether Dr Horvath felt that the blood volume change is entirely due to a hemoconcentration, loss of plasma from the blood, or whether there is a reduction in the total number of circulating cells.

Horvath No

Edholm In other words, we know there is hemoconcentration in the cold Do you feel that that reduction in plasma volume accounts for the whole change in blood volume?

Horvath No I don t believe it accounts for the entire change in the blood volume. I am sure that there is a shift from other storehouses, if you wish to call them that, in the lungs and in the liver and probably from the spleen, depending upon the animal used, which will result in an increase in the number of circulating cells but there is no doubt that there is also an absolute diminution in the amount of available plasma, at least in the circulating blood volume. It is that which may have the important role, at least in my own thinking, in terms of the rapid and slow rewarming of individuals whether or not that may be related even more to the length of time that the cooling may occur There is some

question in my mind as to the validity of the assumption that the change in blood volume only occurs during the early part of the exposure to the low environment. I can readily conceive, although I don't see any evidence to that effect, that there may be slow changes in blood volume which may be due to other factors. How this is brought about, I am not too sure, but it may explain the reactions of individuals to rapid and slow rewarming. That is, if an individual has been exposed to the cold for a short period of time and then is rapidly rewarmed, you can see how he can be successfully rapidly rewarmed because he does have an opportunity to fill that increased vascular space with the readily available fluid in the extracellular space. Now if you take an individual who has been exposed for a long period of time and then rapidly rewarm him, apparently that does not occur. You have a suddenly increased vascular space and no way of filling it.

What has happened to this extra plasma water I don't know. It is interesting that if you rewarm these people slowly over an adequate period of time, that water does go back into the circulating fluid. So that there must be some other way in which this water is being immobilized rather than just a shift into the extracellular spaces, and probably also into the intracellular spaces. That is a problem of homeokinesis which I think is very important in terms —

Barton You have a large diuresis, and get rid of a lot of it.

Horvath Yes, but that diuresis is one which I am not too happy about, because I don't see that diuresis lasts for a very long period of time. When we measure this diuresis, what do we do? We take an individual from an environment like this, a rather hot and muggy environment, and we thrust him into the cold, and he has a diuresis which may last for let's see, two hours.

Barton If you keep him there, it will be two days.

Horvath Well, we kept men there for two weeks and longer and the diuresis was there during the first portion of the first day but we saw no further evidence of diuresis on the succeeding thirteen or fourteen days.

Fremont Smith You did not give him any fluid to drink?

Barton Their intake goes down.

Fremont Smith Yes.

Barton If you make a balance, you will find that he has got rid of a big balance of fluid.

Blair I should like to ask this question. When you kept the men in a cold room for two weeks, did the decreased blood volume and hemoconcentration remain unchanged? In animals we have observed an initial decreased blood volume and hemoconcentration, and then after several days both returned to normal.

Horvath Exactly.

Blair And when the blood volume and hematocrit returned to normal, the diuresis became negligible. We wonder if the diuresis isn't largely a factor of water transfer from the vascular bed. At least in all of the cold-exposed animals where we have carried out blood volume, hematocrit, and water-balance studies, we observe maximum diuresis, maximum decrease in blood volume, and maximum hemoconcentration during the first day of cold exposure, after which all three slowly return to normal and remain normal throughout two months of cold exposure.

Horvath We observed something similar to that as far as changes in hemoconcentration and blood volume are concerned namely that there was on the first day a rather marked change, on the second day the change was less marked and by the fifth day of exposure they were back down to what they were before they were exposed to the cold. But the water balance studies that we made at that time which were admittedly somewhat crude, indicated that the individuals really had no real diuresis after the first day or a portion of the first day However that may be, the changes that we observed in the blood volume were not enough to account for any large portion of the fluid intake or the balance during that four-day period

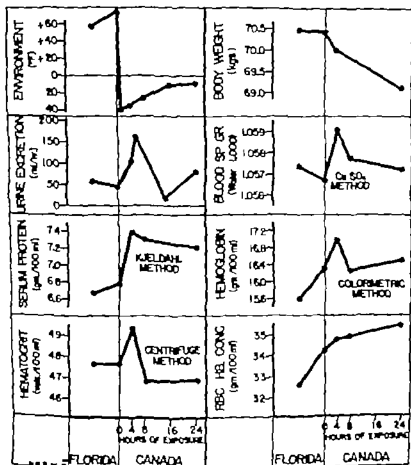
Blair I should like to bring up one point that may be pertinent here. In human subjects — and it is also true in animal experiments — the blood-volume change and accompanying diuresis depends upon whether the subject is left continuously in the cold or is intermittently removed from and returned to the cold room. In subjects left continuously in the cold, the initial decreased blood volume, hemoconcentration, and diuresis begin to return to normal after the first day and eventually are maintained at normal values despite prolonged continuous cold exposure. However if the subjects are removed from the cold room six to eight hours daily a cycle of hemodilution and hemoconcentration is set up, accompanied by increased water intake and increased urine output.

Horvath Yes the one I was describing was where men stayed continuously at −22 F for a period of up to two weeks, so this was an observation after continuous cold exposure.

I think it is true — and this we have observed in man as well as in animals — that if you take them out overnight and give them a chance to recover and then use them again as experimental subjects, you see on the next day diuresis which again lasts over the time you study them. We usually studied them for three hours, and there was diuresis during that period of time. That would continue for months, and they would get diuresis every time they were exposed But people who are exposed continuously to this low environment apparently have a diuresis which is rather short lived

Kark If you have individuals living in a naturally cold environment, such as the Shilo study (3) during the first day of the cold there was a

marked diuresis (Figure 21) and during the second day there was one which probably occurred but which probably was not statistically significant.



Ordinates Environmental temperature (°F) body weight (kg.) urine excretion (ml per hour) specific gravity of the whole blood (distilled water 1,000) concentration of serum protein (gm per 100 ml) hematocrit (packed red cells, ml per 100 ml whole blood) and mean corpuscular hemoglobin concentration (gm Hb per 100 ml red cells)
Abscissae Florida average hours of exposure to cold in Canada

FIGURE 21 Acute exposure to cold-water balance. Reprinted by permission from *Survival in the Cold* U. S. Medical Nutrition Laboratory Report No 13 Nov 30 1948 (Page 32)

Talbott Is this exposure continuously to the same temperature?

Kark No because these people are in a natural environment. The temperature is fluctuating

Talbott This is in the North?

Kark Yes

Talbott But aren t they living in a temperate environment during the ten or twelve hours that they are in their igloos or in heated shelters?

Kark No our people were always cold at night. They always woke up, and they were uncomfortable and shivering

Talbott Weren t they in sleeping bags?

Kark Yes but they never slept comfortably through the night. Few of our subjects ever slept the night right through without getting cold.

One thing we did find was that there was a direct relation between hemoconcentration and ambient temperature the more concentrated the blood, the lower the ambient temperature and as temperature fluctuated up and down, the hemoconcentration fluctuated up and down. In other words, as it got cold the blood became more concentrated as it got warmer it became less concentrated (Figure 22)

Fremont Smith Is there any reason to believe that the diuresis cannot account for the reduction in blood volume, since it starts right away?

Horvath Well, all I can say to that is that the experiments which were done were as well controlled as they could possibly be under the situation.

Talbott Did you determine interstitial fluid volumes?

Horvath No, all we did was Evans blue for blood volume, and hematocrit and plasma proteins and red cell count.

Talbott I think the answer to this problem lies in deuterium studies or fluid space studies.

Horvath Yes.

Fremont Smith What was your conclusion on the time relationship between diuresis and reduction of blood volume?

Horvath The reduction in blood volume persisted after the diuresis was over

Fremont Smith But the diuresis came first?

Horvath The diuresis came first, and the blood volume, which we measured at the end of the first twenty four hours, showed a reduction in plasma volume.

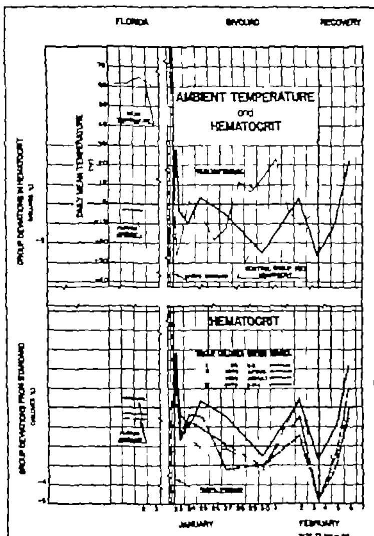
Fremont Smith Was the diuresis enough to account for it in terms of cc.?

Horvath No The diuresis was a little more.

Fremont Smith The diuresis was more than enough to account for it?

Horvath That is right.

Fremont Smith Then is there any reason to assume that the diuresis is not related directly to the reduction in blood volume, the blood volume



HEMATOCRIT IN RELATION TO AMBIENT TEMPERATURE

Ordinates Upper figure—*Daily* mean temperature in degrees *Fahrenheit*.
Lower figure—Average group deviations in hematocrit, expressed as percentage of the Florida value

Abscissae Day of experiment in Florida, bivouac and recovery periods
The air route of the test troops is shown from Tampa, Florida, to Rivers Air

FIGURE 22. Hematocrit in relation to ambient temperature Reprinted by permission from *Survival in the Cold*, S G O. Medical Nutrition Laboratory Report No 42, Nov 30 1948 (Fig 23)

therefore following the diuresis? In other words, why aren't they having a mild diabetes insipidus, where you have a kidney diuresis and a reduction in blood volume, and you try to catch up with it by drinking?

Horvath Because if you continue to measure their fluid intake, you find that they are actually in a deficit as far as the fluid intake is concerned.

Fremont Smith That would not prove that the diuresis was not primary to the reduction of blood volume.

Horvath No

Fremont Smith In other words what is the evidence that the fluid was in the tissues rather than in the urine?

Horvath The only evidence that the fluid was in the tissues comes from animal experiments in which the water content of the tissues was measured. So that, reasoning from other evidence, we would say that there is a shift in the fluid into the tissues

Fremont Smith But the human experiments could be accounted for by themselves as a primary diuresis from cold and a secondary reduction in blood volume.

Horvath On the basis of the fact that no extracellular fluid measurements were made, you could make that assumption.

Burton Aren't you perhaps confusing two things — the shift of the fluid from the tissues into the blood stream, if the animal is cold, that is, in hypothermia, and the diuresis, which I think is best shown in man? I think everybody agrees that the diuresis happens, decreasing the blood volume and that it is a reflex of some kind through hormones. In this case the man's core temperature is not abnormally low I admit that there is good evidence that when the animal is cold, that is, has a hypothermia, there is thus shift but would you maintain that even where the animal has normal core temperature that he has this shift into the tissues?

Horvath If you wish to say that the normal core temperature is above 35 C, yes

Burton Well I would.

Horvath Well, then I would say yes

Burton There are two other things I should like to mention about this effect on fluid balance and loss in cold, and one of them is that on the first day of going into the cold there is a remarkable lack of balance of calories In other words, the subjects eat a lot more than they burn, in the period coincident with the diuresis, as though they were replacing water by body solids And the second thing is the result of just one other interesting observation Dr Bazett (4) made he interrupted the experiment by putting the subjects into the cold for one day The diuresis began, and he then put them back into the warm. The diuresis went on during the second day back in the warm. This certainly indicated a slow action, which made one think of pituitary hormones.

Kark I shall talk about the calories tomorrow but my feeling is that it is not only on the first day that they eat more calories they eat more calories than usual for many more days.

Burton Yes but there is a lack of balance. During the first few days they eat much more, but it is not accounted for by their burning it There is a storage of calories corresponding to the loss of water so to speak.

Kark Well, it may be due to something else.

Crismon Do you have data on sodium balance in men during diuresis?

Kark Do we have data on what?

Crismon Are they in negative sodium balance during diuresis?

Kark No There is transient retention of sodium

Allen What happens to the body weight, and what is the magnitude of change in blood volume?

Horvath It is somewhere between 500 and 800 cc.

Allen That is the maximum?

Horvath Yes.

Burton The weight goes down, but not as much as does the blood volume, indicating again that the subject is eating more food than he burns.

Horvath Excepting that these individuals — I am just trying to recall the experimental background now it has been five years since we did this — were on a constant diet all the time both before and during their exposure to cold

Burton It makes a big difference

Horvath It was slightly under 3,000 calories slightly under what Dr Kark found necessary

Kark Three thousand calories are all right if they don t do any work. For resting men, 3 000 calories are all right.

Horvath They worked a while, not a great deal — two hours a day The rest of the time was spent shivering, if you want to call that real work, that is, in terms of calories.

Bebake What is the reason for the diuresis?

Horvath There are several possibilities. One Dr Burton mentioned namely a reflex phenomenon that may be related to the pituitary

Bebake But isn t the amount of fluid that is lost equal to the amount of blood that is shunted away from the skin, approximately?

Horvath No, because they also lose body weight

Burton One definite thing, Dr Bebake was that we had measurements of the minimum blood flow of the fingers, and we had infrared photographs of the veins, and until one had diuresis and lowered the blood volume, one could not produce as minimal a blood flow in the fingers as one did after it had happened Moreover the veins definitely showed in those two or three days, that they get more and more con-

Talbott That was the potassium excess, not the total?

Kark Yes.

Crismon Forty mEq is as little as you can lose without extreme oliguria.

Talbott You probably are talking about added potassium loss, not total potassium loss.

Conn Negative balance

Talbott Or negative balance, rather

Kark Negative balance

Talbott Not total

Kark No I think I am talking about total in that experiment.

Talbott That is low

Crismon That is astonishingly low

Kark That is potassium excretion I will have that data for you tomorrow I can never recall the data exactly

Talbott Sodium and potassium exchange studies might be informative.

Kark We shall have that data for you.

Talbott This may be irrelevant, but in your studies of cold injury was a transient albuminuria noted?

Kark No

Talbott In our studies on cold immersion we noted albuminuria of short lasting duration.

Horvath There was none in these cold air exposures. Neither was there any in yours, was there?

Kark No

Horvath One of the other aspects of temperature regulation, or the homeokinetic problems associated with it, is related to blood sugar levels, which is really quite a fascinating sort of thing We do know that you can stop shivering, which is part and parcel of temperature regulation, by giving the animal insulin, or by giving man insulin, and making him hypoglycemic, and yet there is, so far as I know very poor evidence to the effect that there is a hyperglycemia in the cold. Some of the German experiments indicated that there was a hyperglycemia, and I believe in one case, of one shipwreck survivor a hyperglycemia of about 300 mg per cent was noted As far as I know those are the only bits of real evidence in man that there is a hyperglycemic response to cold. It would be a rather interesting thing to study because it may be related to the epinephrine response, or it may be related to the shivering. Certainly they are not hypoglycemic otherwise the shivering would stop So it leaves you free to speculate as to the relationship of the regulation of blood sugar levels to the adaptation of man to a cold environment.

Fremont Smith Do you mean there are inadequate data or that the data show no change?

Horvath Both. That is, there are inadequate data, and they are on both sides The few experiments that the Germans did indicated that a rather striking hyperglycemic response occurs, and out of a group of ten shipwreck survivors there was only one that had a hyperglycemic response. The others were within normal levels. Unfortunately in this latter group so many factors were involved that the picture obtained at a recovery hospital may not be valid. There have been a few experiments done on animals which show that it does increase, but those are rather inconclusive.

Barton The root of the difficulty in the experiments is that most people feel that they have to give an anesthetic in submitting animals to extreme cold. Once you give an anesthetic —

Fremont Smith Are you visualizing animal experiments now? I was visualizing human experiments

Talbott In connection with an elevated blood sugar level, Dr Siple has an interesting observation from the time that he spent in the Antarctic.

Siple A medical officer on one of our Antarctic expeditions passed on the physical condition of all of the other members of the expedition before departure. He failed, however to report his own condition. It was discovered later that he was mildly diabetic. He knew his own condition and took along a supply of insulin. He was perfectly capable of carrying out his duties An interesting thing was that although the winter night camp had aggravated his condition, when he became exposed to a great deal of cold in the summer he was able to eat all types of foods and sweets without any regard to his diet, and to discontinue use of insulin. As soon as he got back to normal indoor living again, where he was warm and relatively inactive, his diabetic symptoms resumed and he had to start using insulin again

Part of this story is recorded in Dr Frazier s report of the U.S Antarctic Service Expedition.

Kark I thought he got worse. Didn t he get worse?*

Siple No He went out on a trail party by dog team. He was out for a period of about three months, and during that whole time he was able to eat things that he had not eaten for a long time, that is, sugars and chocolates which reportedly had no ill effects. But within a short time after he got back into the relatively warmer main camp he had to revert to his insulin, as his diabetic symptoms recurred

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* Dr Kark *impression was not entirely in error Dr Frazier reported that his first sugar* spillover had occurred about two years before the expedition, and after six months' diet he had apparently recovered About two months after reaching the Antarctic he had reoccurrence of sugar spillover and had to start resuming insulin. However, the incident which I related occurred the next summer as second period of apparent recovery Thus Dr. Kark summary of total effect of the Antarctic experience on Dr. Frazier diabetic condition could be interpreted as adverse, and it was therefore perhaps only the unusual activity of summer that kept his blood sugar down — Dr. Siple

Horvath And activity?

Siple Yes more sedentary than while on the trail.

Talbott Was he on a higher fat diet when he was on the trail?

Siple Yes

Kark Now I remember the story It is in the *Proceedings of the American Philosophical Society* (5) He had diabetes, he went to the Antarctic, and he went out on trail and did not have diabetes when he got back into camp his diabetes was much worse.

Siple I don t know about his being much worse. At least, my recollection from being there was that he was not apparently much worse than before he went out on the trail, because there was no physical effect at the time that was observable by his companions.

Kark He had to take more insulin.

Siple He had to start taking it, at least I don t know if he took much more than he had previously

Kark It is a long time since I read that.

Burton Mr Chairman, may I go really fundamental on you, so to speak?

Talbott Yes

Burton I want to take this opportunity to talk to this group of people who are interested in these problems

I feel that perhaps in the next five or ten years we will turn from examining the mechanism of temperature regulation, on which a great deal of work has been done to studying the fundamental control of the level of body temperature and undoubtedly it will be at the endocrines that we shall look. And I feel that we need much more information about the diurnal rhythm of body temperature and how it can be altered. Already we know of some endocrinal influences that can alter this. I think that most patients that have pituitary abnormalities will be found to cycle usually a little lower than the normal body temperature range It is a fairly good clinical cue, if you see a chart where it is cycled below the red line, to think about the pituitary Then, too, we know in the case of the menstrual cycle in human beings that there is a remarkable change of diurnal rhythm during the ovulation period, which is now used practically And we do know — it has been reviewed recently by Kleitman — that this diurnal rhythm is not completely explained, or is only partially explained by the routine of exercise and meals, and so on (6) If you reverse that routine of exercise and work in the night instead of the day it takes many days before the diurnal temperature rhythm gets into the new phase

I feel that although some old work has been done on this, today with transatlantic flights and transcontinental flights which get you to a place where there is four or five hours difference in time, and during which

your routine is changed, there is a notable opportunity to get much more data on what happens to the diurnal rhythm when you fly across the Atlantic or even when you fly across the Continent. I should appreciate it if people here who are making transatlantic flights — I know most of you will at some time or other — would be interested enough to take your — I will say oral rather than rectal — temperature every four hours for two or three days before the trip to establish what your diurnal rhythm is. One should continue to do this faithfully on the flight, and follow it, say for a week when you get on the other side, because we need much more information.

I would also be interested, in two or three years, in finding somebody who is going to spend the winter up North in the twenty four hours daylight or darkness, summer or winter to see if anything happens to the diurnal rhythm Evidently it is one of these fundamental biological rhythms which is not easily changed, and one which I suspect might have to do with the cycles of light and darkness. I do feel that this is a direction in which we could get some very fundamental information about temperature regulation. If any of you should do this, send the data to me or even to the Macy Foundation. We would put the information together to see if we had something of interest

Talbott Have you checked McFarland's article that appeared in 1937 He went to Hong Kong with the Pan-American Airways, and reported observations which included four-hour urine outputs. I believe that he observed body temperatures also (7)

Fremont Smith Ross McFarland?

Talbott Yes.

Horvath Dr Burton accused me of not reading the *Journal of Applied Physiology* six months from now and I am going to accuse him of not reading it a month from now because part of it is to appear in the *Journal of Applied Physiology* a month from now

Burton Years behind.

Fremont Smith You are supposed to be at least six months in advance.

Horvath It is very difficult to change the diurnal rhythm

Burton Yes.

Horvath We are reporting something of that sort shortly We have studied the diurnal rhythm in twenty people over a period of time to get the pattern and to see what it amounts to in comparison with all the work that has been done in the past on one or two people We changed the living habits of our help over there, part of them being nurses. We had them shifted to the night shift — against their better judgment, I assure you — and also shifted some of the staff to night duty After two weeks —

Fremont Smith Against their better judgment too

Horvath Yes, I am afraid it was, but they had very little to say about it.

Burton This might be quite different. You see, when you fly across the Atlantic the element of light and dark periodicity has changed with you, with your routine. When you fly across the Atlantic, your experiment is really a different one.

Horvath In Kleitman's experiments, in which he placed the subjects in a cave, one of the two subjects — not himself but the other — refused to make any alteration, if I recall. Also I think Ross McFarland's data do not indicate any shift

Burton Has anybody any information as to the diurnal rhythm in people living through the polar night?

Behnke Dr Kleitman is now in Norway and is making the tests that you suggested. Some information should be available by late summer. Of course, you know of his work with the Navy in which the diurnal rhythm was abolished in watch standers who continually rotate their watches so that they never work at the same time during a twenty-four hour period on successive days

Burton I don't know whether it is related, but it has recently been shown that schizophrenics have their rhythm abolished Perhaps you are making him a schizophrenic.

Behnke There is known to be chronic fatigue in the Navy and it is associated with excessive coffee drinking, to keep awake.

Siple When you speak of it being difficult for this rhythm to change, is that a matter of days weeks, or months?

Burton The reports are rather varied. I mean, in some people, apparently it may take weeks in others it is changed in three or four days. It certainly does not change right away when you change the routine in anybody does it?

Horvath Of the twenty people we studied, nobody changed within two weeks, and some of them had not changed at the end of a month, when we had to quit. We could not go much longer than a month. At the end of that time some of them had still not reverted to a complete shift in their diurnal cycle.

Burton I apologize. This really is not relevant to the Conference.

Fremont Smith Yes, it is

Burton I wanted to take the opportunity

Talbott No apology need be offered.

Horvath Let us discuss another point in the homeokinetic response. There is this very interesting business of cold sensitivity which, of course, gives you some rather extraordinary changes as far as the reactions of the body are concerned a marked urticaria, an initial rise in blood pressure, an initial rise in the pulse rate, flushes, headaches, painful and stiff

joints, and so forth and so on, and finally ends in a syncopal attack. It may be due to histamine or it may not be but there is certainly an aspect of the homeokinetic reaction which ought to have a great deal more emphasis placed upon it than it has had in the past. There have certainly been only a few scattered reports as to this type of response primarily by Horton It has also been suggested in several other reports that this type of response might explain some of the sudden deaths which occur in people who are swimming in cold water

Siple That cold sensitivity — is that owing to blood pressure changes?

Horvath Apparently it can be induced by a very minor sort of stimulus. It is not a painful stimulus Exposure of the hand to water of only 10 C. will, in a number of individuals, induce this type of response, which is a rather extreme indication of a failure of the homeokinetic reactions. It is quite remarkable, really if the descriptions of the particular response are true

Fremont Smith But isn t it more than a failure of the homeokinetic response? It is a positive want of response in addition to failure isn t it?

Horvath Yes, but we consider it as starting off as failure to make a response, which then goes on to its ultimate which is —

Fremont-Smith Maladjustment

Horvath — maladjustment or utter failure of the organ So it is initially a failure of homeokinesis.

Fremont Smith You don t end up with an individual who just did not respond at all you end up with an individual who has responded in a very positive but bad way to cold?

Horvath Right

Fremont Smith I wanted to emphasize the positive response rather than the absence of the normal adaptive responsive There is a mal adaptive response in addition to failure to make the normal response.

Horvath But apparently a response which can be so trained — perhaps I should not use the word trained — as to enable the individual not to make the final maladjusted response.

Fremont Smith What do you mean?

Horvath That is, some of the experiments employed repeated histamine injections and also continued exposure to 10 water and the results obtained indicate that you can take an individual and pull him out of this cold-sensitivity response so that he responds just as anybody else does, just as you or I would

Fremont Smith You mean you can get over it?

Horvath You can get over it

I can only judge this from the literature that is available on it but it certainly would indicate that more interest and emphasis should be placed upon evaluating this type of thing, because it is a very nice indi-

cation of how you can get a normal — I don't like the term "normal" — but at least a usual homeokinetic response where you did not have it earlier

Fremont Smith I believe Harold Abramson reported a case in which he found psychological factors precipitating the cold allergy which had not been present before and which cleared up under psychotherapy quite dramatically He saw it as a psychosomatic behavioral response. That was within the past two or three years I think it may be in *Psychosomatic Medicine* I shall try to check up the reference on that.

Burch We studied one patient who had cold allergy (8) If one finger or the whole hand were placed in cold water at 18 C., an extensive edema developed We constructed a tonometer (9) for measuring the tissue tone and change produced by edema, which is an expression of tissue pressure The tonometer values correlated with the degree of exposure to cold

This patient also had many emotional factors influencing her reactions She was more apt to develop disturbances when she was having difficulties in her home life. Of course, such is probably true of many allergic states

Fremont Smith I think in Abramson's case the psychological mechanism was brought out quite clearly to the patient, and then the patient was no longer allergic to cold It was quite a dramatic recovery as I remember it. It started off dramatically and it ended dramatically

Horvath It may well be that in the experiments that Horton has carried on he has brought the patients back by a form of psychotherapy and also by reconditioning them That may be it We still do not know

Fremont Smith I thought of that It is a form of psychotherapy

Horvath A form of psychotherapy

Fremont Smith Also reconditioning

Horvath That may be it entirely but still we don't know

Fremont Smith No It is well worth studying

Kark Dr Sussman of Johannesburg told me that the native African troops, the Zulus and other Bantus, were extremely sensitive to cold. I was going to talk about this tomorrow but we may as well talk about it now Many of the African troops developed urticarial wheals in response to cold showers Whenever they gave them cold showers, a very high percentage of them broke out in urticarial wheals. That is not in the literature at all That is just his statement to me

Fremont Smith Can you identify that by time and place for the reference that is where the observations were made and in what year?

Kark That was told to me in 1945 at the time when Sussman was running the peripheral vascular unit of the South African Army Medical Corps

Fremont Smith Thank you.

Horvath Were those troops still in South Africa or were they somewhere else?

Kark No, these were in Africa. They were Zulus and Bantus, and were taken from tribal life into Army camps. There, of course, they took cold showers, which apparently they were not accustomed to.

Fremont Smith You mean they were given cold showers.

Kark They were given cold showers.

Gottschalk I know of a physician who breaks out with urticaria if she stays in the water over a certain period of time, and at one time she had to have a tracheotomy.

Fremont Smith Angioneurotic edema.

Kark I suppose you were going to mention cold agglutinins?

Horvath I was going to mention them.

Kark They are very interesting. The cold agglutinins which produce hemolytic anemias also are disturbances of the same type, and we just don't know where they come from or exactly how they work.

Fremont Smith And there is a hemoglobinuria. Is that what you are talking about?

Kark Yes.

Horvath I think that is all we can say about it, because we don't know much more. It does occur, and it is accompanied by hemoglobinuria.

To bring in the nervous system, I thought I would start off by mentioning the ability to induce anginal attacks in patients by similar types of exposure to cold, such as was done about 1946 or 1947 — by Friedman, I believe it was. He was able to induce an anginal attack by exercising individuals who were suspected of having angina pectoris. He was also able, interestingly enough, to induce that same type of anginal attack if he exercised them in a comfortable room and placed an ice cube in their hand, whereas just simply holding the ice cube had no effect, so far as inducing an anginal attack. It may be related, of course, to the problem of exercise more than it is to the problem of cold. But it is remarkable that a great percentage of the patients had an anginal attack when exercising in a warm room while holding an ice cube in their hands, whereas they did not have an anginal attack when they just exercised in the warm room without a cube of ice.

Barton Did it work if the ice cube was in a glass?

Horvath I think not.

Fremont Smith There is a very marked vasomotor reaction to holding an ice cube in the palm of your hand for any length of time.

Horvath Yes.

Fremont Smith I am sure there would be a fall in skin temperature in the opposite hand, and therefore it seems to me not inconsistent that this

could be a genuine thing Weren t their experiments with the drinking of ice water?

Horvath Yes.

Fremont Smith I always felt that the cold was complicated by the mechanical distension of the stomach. But I remember that someone—

Horvath Cannon.

Fremont Smith Walter Cannon?

Horvath Yes

Fremont Smith In human beings?

Horvath Yes

Fremont Smith Somebody did it more recently within five years. In susceptible individuals he occasioned anginal attacks by having them drink ice water

Kark No when they drank ice water there was vasoconstriction of the blood vessels in the hand. Isn t that right?

Blair That is correct.

Fremont Smith I am thinking of another experiment. I don t think it was Robert Levy but one of the cardiologists here in New York, if I remember rightly in the early days of World War II conducted an experiment in which the subjects drank about a liter of ice water and got quite definite anginal attacks

Horvath I have not come across that one at all.

Fremont Smith They were attributed to the cold water in the stomach. I cannot give you the exact reference

Talbott You mean directly to the cold water, or attributed to a reflex with increase in blood pressure?

Fremont Smith Attributed to the cold water in the stomach

Talbott Directly?

Fremont Smith Well, I don t know what you mean by directly

Talbott Just simple drinking of water will cause an inversion of T waves

Horvath Well, so many things will cause an inversion of T waves.

Fremont Smith At least that is consistent

Burton That is probably a local effect of cooling that side of the heart That is probably the explanation.

Fremont Smith It could be But if you get, as someone showed, vasoconstriction in the hands from drinking ice water then you are dealing with a general response to cold, just as if you placed the individual in a cold environment.

Burton Of course, there is a group of experiments — Hamilton did them — on cold on one side of the heart (10)

Horvath Hamilton and this chap up in Vermont, under one of Robb s men, have been doing that. They have been measuring the temperature

of various parts of the heart, putting thermocouples on it, as they poured ice water down a dog's esophagus and let it rest in the stomach. They were able to find that there was an inversion of the T wave upon drinking of the ice water and that there was also a cooling of the heart itself, which would probably account for that sort of thing.

Fremont-Smith: Isn't that amazing for the circulation to the heart?

Burton: The T wave is supposed to depend upon the balance of what you are picking up between the two halves of the heart. If you slow one side, you invert the T wave.

Fremont-Smith: I was amazed at the perceptible difference in temperature in such a vascular organ as the heart induced merely by the presence of cold water in the stomach.

Horvath: That is no problem at all. It is very easy to change the temperature of the heart by almost any application of heat or cold. The first rather nice piece of work was done by Hamilton in the early thirties. He allowed some fluid to drop into the thoracic cage, and was able to show that there was a difference in temperature on the left side when fluid was allowed to drip into the right side. Since then a great many investigators have shown that it is easy to influence heart temperature and cause this apparently primary inversion of the T wave as a consequence of altered temperature gradient between the two portions of the heart.

Behnke: Dr. Horvath, are you talking about an isolated phenomenon or something that is relatively common? You don't confine your remarks to ice water?

Horvath: No.

Behnke: I am not looking for support in favor of drinking ice water but when you consider all the people who drink iced fluids and get along all right —

Horvath: The point is that if you have an inverted T wave, it does not mean anything at all. You see, you can have a thousand and one inverted T waves and get along very well.

Behnke: With anginal attacks you would certainly have an expression of pain. I have not heard of anybody developing anginal pain from drinking Coca-Cola, beer, or beverages with a little more alcohol in them.

Horvath: That was the experiment you were trying to recall, Dr. Fremont-Smith.

Fremont-Smith: It was a liter of ice water drunk fairly rapidly, I believe. I always thought it was rather redundant. They were patients who had some kind of coronary illness, and the experiment was to be comparable to the exercise experiment and comparable to the exercise-under-anoxia experiment to bring out the myocardial insufficiency.

Birch: You can reverse its direction by not changing the temperature very much.

Horvath A traction of a degree

Lupeshkin has found that changes in the neighborhood of only two- or three-tenths of a degree are sufficient to produce that pain.

Burch The influence of cold on the process of repolarization has been known for many years It is because of this influence that it is difficult to study the T wave when the animal s chest is open and the heart exposed to the atmosphere The T wave may become inverted. Just recently during high speed motion-picture recording of mechanical and electrical activity of the heart, the T wave was first sharply inverted when the lights were turned on to record the motion picture, the T wave, in the space of one beat, became upright apparently owing to the heat from the lamps.

Barton I think the cardiologists have tried to exaggerate the importance of whether our T waves are upright or inverted don t you? I mean, after all, there are so many ways physiologically that they can be changed Of course if none of those factors are present and you have inverted T waves, perhaps you should worry

Allen You should take out the perhaps

Barton Perhaps having inverted T waves because of these other factors does not mean that the factor is injurious.

Burch The T waves are inverted merely by physiologic processes, such as filling the stomach with cold fluid Persistently inverted T waves are usually not normal This whole problem is too complex to discuss briefly

Barton There is one other factor we should discuss in this connection. Isn t it very definitely known that asthmatics often have violent attacks when breathing cold air or when put into the cold?

Fremont Smith And hay-fever sufferers

Barton Yes

Fremont Smith In hay fever that is very characteristic.

Barton In hay fever there is a reflex from the upper respiratory system (11)

Fremont Smith Opening an ice chest will precipitate an attack in patients with hay fever When they open an ice chest to get something out, and close it again just that breath of cold air will precipitate a severe attack of hay fever sneezing, coryza, and everything else And those go together with the asthma very often.

Horvath Dr Burch just mentioned to me in an aside that all you have to do is put your bare feet on the floor and you induce an attack. I think that is a very pertinent point

Fremont Smith I think there was an experiment by Mittleman and Wolff some years back, at Cornell Medical School with patients with Raynaud s disease, and they found as is well known, that by lowering

the temperature in a constant-temperature chamber they could precipitate attacks. They also found that at a temperature which did not precipitate attacks, attacks could be precipitated at will by discussing with the patient emotionally disturbing experiences. They also found that the normal individual would get a drop in skin temperature when emotionally disturbing experiences were discussed, that those with Raynaud's disease could be thrown into a complete attack. Then they found a further factor on days when the patient was in a reassured mood, when everything was well at home it required a greater degree of temperature drop in the constant temperature chamber to precipitate an attack, while it required less of a drop in constant temperature on a so-called anxious day when things were more tense in the home situation

You had there, apparently a summation between the influence of anxiety on the sympathetic nervous system and the influence of cold on the sympathetic nervous system I think these factors of summation should be very well considered They are particularly pertinent I think, in the Armed Services, because you have perhaps three things that may concatenate in terms of summation cold, anoxia, and emotional tension or anxiety and it is quite possible for all three to take place simultaneously I think, also that we should not neglect the emotional tone of the experiment, or of the experimenter to the experimentee as an added factor when a patient is being exposed to a variety of experimental situations, including exposure to cold

I think that the psychological meaning of the experiment I know Alfred Cohn — and who else was it that was working with him?

Burch I did, and Neumann joined us about one year later

Fremont Smith Am I right in this? As I remember the experiment, as Cohn told it to me, you found, in measuring the pulsations in the finger in the plethysmograph, that you were not getting just normal plethysmographic responses, but plethysmographic responses in a laboratory setup with much apparatus around. Neumann told me that they quite happily had solved that by building the laboratory to look like a boudoir with no apparatus showing at all They felt they had solved it, but we pointed out to them that they were then only observing fingertip responses to the environment of a boudoir and not to the normal

Burch Dr Burton can verify concepts of the volume changes in the fingertips. They are very sensitive to psychological factors During the recording of a plethysmogram of the fingertips, the noise of dropping an object outside, the ringing of a telephone or a frown at the subject, results in extreme and immediate vasoconstriction The problem of multiplying three by three or merely asking the subject his name may result in vasoconstriction.

Burton I was very much mortified when I learned this years ago



Figure 23 Experimental observations during hypothermia

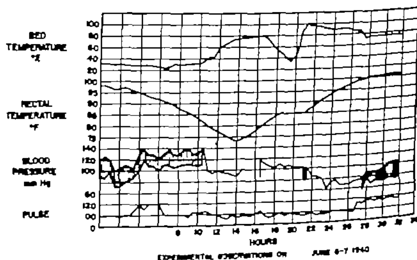


Figure 24 Experimental observations during hypothermia

blood pressure, both diastolic and systolic phase This is followed by considerable fluctuation and eventually a gradual falling off of blood pressure, at times to a level that cannot be recorded by a mercury manometer The radial pulse was also unobtainable at these times. The brachial artery was just palpable. The femoral pulsations were always present.

After the initial increase in pulse rate, this also decreased and in some patients reached a low of not more than forty beats per minute.

The data from a patient who was observed for approximately thirty hours are given in Figure 24 The core temperature in this subject reached a minimum of 74 F at the end of fourteen hours. This is in the same range as that of the famous Chicago lady who was taken out of a snow bank. I think her temperature was 71 or 72 F

The heat regulating mechanism of the body is presumed to cease operating at internal temperatures below 75 F and loss of body heat takes place afterwards as if the body were an inanimate object (1) Certainly we noted that there was a continued effort on the part of the body to restore internal temperatures at all levels above 75 F As soon as the circulation of brine through the blankets was interrupted, following a lag, the internal temperature began to rise. Depending upon the level at which we wished to maintain hypothermia, circulation was resumed and the internal temperature of the body depressed

In this experiment there was an initial and a secondary rise in the blood pressure. Subsequently the blood pressure was unobtainable for a period of time.

In addition to the changes in pulse, blood pressure, and internal temperature, I wish to discuss this morning renal clearance studies. These were completed in some subjects during the period of induction, in others when the internal temperature was at a minimum, in others during restoration, and in all patients several days after recovery from hypothermia. Glomerular filtration rate, renal blood flow diodrast Tm. and glucose Tm. were observed You will recall that these studies were done more than ten years ago, at which time diodrast rather than P.A.H was the experimental substance for determining blood flow and Tm.

Barcb Are you upset when the blood pressure is unobtainable? Aren t you frightened that something serious may happen to the patient?

Talbott One needs courage to perform experiments such as these. Changes in cardiac rhythm were observed that were very distressing I do not have the electrocardiographic tracings with me but auricular fibrillation was observed from time to time in patients who had a negative cardiac history The cardiac arrhythmias were present when the core temperature was below 85 F during depression or maintenance.

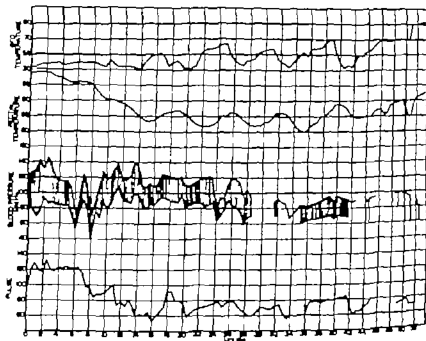


FIGURE 23 Experimental observations during hypothermia

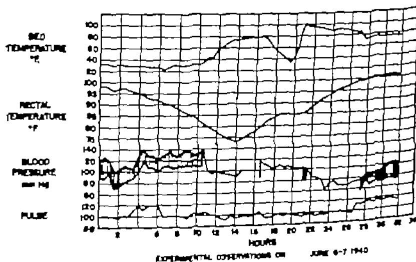


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As soon as the internal temperature was permitted to rise, a return to normal rhythm was observed.

One reason why we were not as concerned as possibly we should have been during the periods when blood pressure could not be obtained was the fact that we were always able to get a good flow of arterial blood from the brachial or femoral artery The blood for chemical analyses was taken by arterial puncture after induction simply because it was so difficult to obtain blood from the venous channels. At times a needle was inserted in a vein and some blood was removed, but usually the quantity was inadequate for our purposes So long as we obtained arterial blood by arterial puncture, we knew that blood was flowing through the deep tissues at least

Gottschalk What was the level of consciousness and responsiveness of the patients?

Talbott The patients reacted as if they were heavily sedated. There was frequent mumbling They were aware of pain when we were collecting blood samples They registered some objection to urethral catheterization which preceded the renal clearance studies. Once the infusion for the renal clearance studies was functioning and the bladder catheterized, the blankets were put back on the subject and the collection period started During a period of three or four hours under such circumstances the patients might sleep without awakening, and we might collect our samples without difficulty

Gottschalk Whenever you did an arterial puncture with novocaine, did that arouse them?

Talbott We did not use novacaine for arterial punctures. We encountered less reaction without local anesthesia.

Minard I believe Bigelow (2) observed cyanosis unless he prevented shivering by giving his animal some barbiturate and artificial respiration. Did the amount of barbiturate that you gave control shivering? If not, at what body-temperature level did shivering stop?

Talbott An effort was made to make observations on shivering We were aware of the work that Burton and Brook had done some years before on the type of muscle reactions during cold exposure (3) We were successful in obtaining electromyographic tracings in some patients. Analyses of these tracings revealed two types There was gross shivering that was visible, as well as fine muscle tremors that were apparent only by electromyography

There was no sedation beyond the initial barbiturate. It is not believed that this was effective after the first few hours.

Fremont Smith Did you have any indication that the duration of the pentothal sedation was prolonged because of th hermia, or do you think that you had got of the pentothal dly in these

patients, and that after four or five hours or less, the patients response was entirely free from the pentothal effect?

Talbott We assumed on the basis of two or three induction experiments only in which the patients became very disturbed after three or four hours, that the action of the intravenous barbiturate was dissipated by this time. We did not believe that there was any significant difference between the action of intravenous pentothal at an internal temperature of 93 F in comparison with an internal temperature of 98 F

Fremont Smith Did the pentothal work in this cold patient as well in the second dose?

Talbott Oh, yes, the action was a striking one. The subject would go to sleep immediately but after the first few hours it was believed that the principal sedation was accomplished by the cold and not by the barbiturate.

Barton Did you have the oxygen consumption?

Talbott Yes, oxygen-consumption observations were made. The average oxygen consumption even in the quiet state tended to be above normal rather than below

Horvath Two to three times in some cases

Talbott Was it as high as that?

Horvath Yes When there was marked shivering, it was three times. In some of the cases, when there was no shivering it was twice as high

Barton That does not agree with some other people s observations

Talbott The oxygen consumption in some patients was three times the preinduction value.

Horvath It was twice the value when they were quiet

Talbott I agree.

Horvath I was looking at the data a while back. It was quite high.

Barton There are some low ones, which indicates to me that there must have been, perhaps, muscle activity

Talbott We had the tracings which showed fine muscle tremors in the absence of gross shivering

Kirk There may be some work of Glickman s (4 5 6, 7) which bears on this point He measured muscle potentials of men sitting in a cold chamber and showed a very direct straight line relationship between the number of the action potentials and the oxygen consumption, even when there was no shivering He has not published this work.

Talbott I am quite willing to accept that

Kirk He has those data

Crismon Do you have figures on the urine volume?

Talbott Only during the renal clearance studies.

Fremont Smith Was there diuresis?

Talbott Since the urine volumes were determined only during the

clearance procedure, we cannot answer the question regarding diuresis.

Crismon That is what I meant.

Talbott We did not collect urine samples at other times. During the clearance procedure at least a liter and a half of fluid is infused, and the diuretic effect is probably unrelated to the change in body temperature.

Crismon That is true, but you maintain the infusion throughout all of the clearance period so that the volume goes down —

Talbott There were no significant fluctuations in urine volume during the collection periods

Barton Did you have any albuminuria along with this?

Talbott Albuminuria was observed in a small percentage of subjects only Most of the urine samples were free of albumin.

Barton By a clinical test?

Talbott Yes. Our observations were not in keeping with some. It is appreciated that the incidence of albuminuria is presumed to be higher during cold exposure

Barton That clinical test fails to give any indication whether or not the albumin is three times the normal range of albuminuria, so it is really inadequate for showing a slight increase. For albumin in normal samples of urine, you find that the probability curve runs out at about 12 mg per cent. The clinical test apparently does not give any indication of a faint trace until you get up in the range of 30 or 40

Misard I was wondering if you measured cardiac outputs.

Talbott These studies were done when catheters were placed in certain orifices of the body but not in all Furthermore, these data cannot withstand the test of having determined inulin or diodrast in the renal vein, and we do not know the extraction ratios

In Figure 25 a linear relationship between the depression in glomerular filtration rate and rectal temperature is apparent Thirteen observations are recorded, and the data are satisfactory

In Table I representative data are given. The glomerular filtration rate may show a maximum depression of approximately 50 per cent with an average internal temperature of 85 F The renal blood flow values show a greater proportionate decrease, and although we do not have extraction data we trust that these are valid observations. The filtration fractions are given in the last column, and may be as high as 30 per cent. The diodrast Tm. is depressed slightly more than the inulin clearance. These data are interpreted as showing marked hyperactivity of the vasomotor system

A single observation which bears upon the solidification of lipids may be of interest. In one subject only in the series, an area of approximately twenty-five centimeters over the buttocks became solid during hypothermia. The patients were turned regularly every hour but in this instance

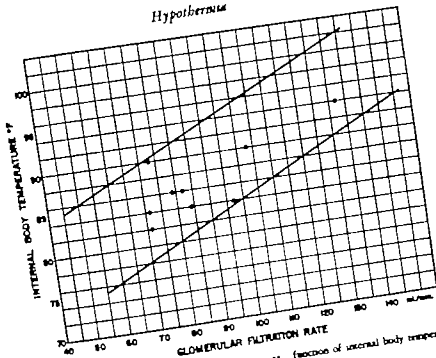


FIGURE 25 Depression in glomerular filtration rate as function of internal body temperature.

TABLE I

Renal Function Studies in Hypothermia

Representative Observations Per 1.73 Sq. M.

	Inulin Clearance cc plasma/min	Diodrast Clearance cc plasma/min	Diodrast Tm mgm/min	Creatinine Clearance cc plasma/min	Filtration Fraction Per Cent
Before	120	650	50	160	18.5
Induction	110	550	15	170	20.0
During (rectal T 85 F)	70	230	25	70	30.0
Recovery	100	500	35	120	20.0
After	120	650	50	160	18.5

the interval was longer Shortly after midnight I was called to see the patient and found this area as hard as wood The patient s temperature was permitted to come back to normal and twenty-four hours later there was no evidence whatsoever of any damage to the skin. I fully expected an extensive skin slough. We believed at the time that the phenomenon was one of solidification of lipids we hoped it was nothing more.

Fremont Smith Was the temperature low enough? It could not conceivably have been frozen. I think that is the most crucial point there.

Talbott The blanket temperature did not permit the skin of the subcutaneous tissues to be frozen.

The aftereffects in this series of patients were not clinically significant. One or two patients had a little edema of their ankles for two or three days following the study Hypothermia was repeated in several patients at three- or four week intervals, and no accumulated untoward effects were observed

Fremont Smith Induced hypothermia.

Talbott Induced hypothermia

In summary approximately fifty hypothermia periods were observed in fifteen patients

Fremont Smith Did you get any psychological remissions?

Talbott We observed several striking changes for short periods of time. In several of the younger subjects who had been sick for not longer than two or three years, in comparison to those who had been sick for ten or twenty years there were significant psychological effects which were transitory In a few subjects significant psychiatric improvement was observed for as long as several days The parents felt in one or two instances that for as long as a year following induction they were psychiatrically improved. I would interpret any change that we have observed as due to a form of shock therapy

Shumacker Did they eat or drink?

Talbott A stomach tube was passed and they were fed by this route from time to time. They appeared to assimilate a liquid diet without difficulty

Conn May I ask about serum electrolytes and blood sugar?

Talbott These data have been published in the article by Dill and Forbes (8) Possibly Dr Horvath will remember the blood sugar values. The data for hematocrit, serum protein, blood volume, and plasma volume showed changes in keeping with dehydration.

Horvath The blood sugars were extraordinarily variable. One or two patients had elevations, but most of them had slight changes. We took the samples of blood depending on whether or not they had had their feeding an hour before or three hours before, so that is quite a variable. We could not say any of the blood sugars were obtained in what would

be considered a basal state, because we were taking the blood samples in no relation to the basal states.

Shumacker Did you do nitrogen studies?

Horvath No

Kark Ketone bodies?

Talbott Yes, we did.

Kark What happened?

Talbott I do not remember There was a significant shift with temperature in the position of the oxygen dissociation curves to the left sufficient to maintain a normal arterial saturation with oxygen Oxygen was not given by mask.

Fremont Smith How much reduction in plasma volume?

Talbott As much as 25 or 30 per cent.

Fremont Smith That meant that the fluid had gotten out into the tissues?

Talbott Yes.

Fremont Smith Do you feel that the reduction in total blood volume was enough to account for the apparent absence of blood in any superficial vessels, or do you feel that there must have been a pooling of blood in a vascular bed within the body which would account for the remaining blood volume? It seems to me it is rather important to know whether your 30 per cent reduction in blood volume was enough to account for the fact that there was no blood apparently in any superficial veins, and often little blood in your limb arteries

Talbott No, I would not say that Undoubtedly there was a significant reduction of blood flowing in the limb arteries. Although pulsations were present in the large vessels, I am confident that vessel caliber as well as flow were reduced On the other hand we know that if blood flows from the arterial system it must be returned by the venous system even though the superficial veins appeared to have little or no blood in them The blood must come back through the venous system

Horvath The deep veins?

Fremont Smith That is the possibility yes

Horvath They must have been carrying it because this was certainly a good flow of blood You had no trouble getting arterial blood

Fremont Smith You could get arterial blood but you could not get blood pressure?

Talbott That is right

Fremont Smith That certainly suggests a good deal less blood in those arteries than there would have been normally

Allen Not necessarily It only means that the systolic thrust is gone when the pulse is gone that is all

Fremont Smith Does anyone have an impression or would you want

to give one Dr Talbott, as to whether there was a pooling of blood—in other words, a vasodilatation in some other vascular bed—that partly compensated for the very marked vasoconstriction in the skin? I raise the question because in typhoid vaccine fever as an example, during the rise in fever there is a tremendous vasoconstriction throughout the skin, and a complete obliteration of movement of blood from any skin that you can see. If you looked at that alone, you would say that it meant an increased peripheral resistance, but actually the blood pressure is falling heavily and it is way down at shock levels at that point. And since there is no change in plasma protein and there is no likelihood of change in blood volume under those circumstances, I think one has to assume that there is a shift of blood from the peripheral bed to deeper beds, which must be, therefore, dilated and vice versa, when the temperature reaches its height, there is an enormous dilatation of the vascular bed in the skin with arterial pulsation in the capillaries, but no change in blood pressure at all from the previous twenty minutes when there was no blood moving in the skin at all so again there must have been a shift of blood

Now whenever a person becomes cold through ordinary exposure to cold—and I guess you had the same thing here—there is a vasoconstriction in the skin and a shunting of blood out of the skin. I am raising the question Is that entirely to be accounted for by a loss of blood volume, or is there a shift of blood into dilated vascular trees somewhere else?

Kark The only data that I know of that have been published on that point appeared in the November issue of *Clinical Science* in a paper by some people from England, Glaser *et al* (9) in which they put people on X ray tables and took very carefully controlled X rays. They showed an enlargement of the liver during cooling, and also congestion of the lungs with increase in the size of the pulmonary vessels however there was no change in the size of the heart.

Shumacker Did you weigh your patients?

Talbott We weighed the patients before the experiment and the day following I believe that the type of experiment described may not be the same as ours, and that exposure to cold without a significant reduction in temperature is a different physiological situation. In our experiment the hypothermia was maintained in some instances for more than two days. The changes may be quite different for shorter periods of exposure.

Kark This was two and a half hours

Talbott Even so I think that this is a different situation. As far as pooling of blood is concerned, I have no explanation. Probably there was some pooling but this did not account for many of the changes observed

Fremont Smith You would not have any idea where it was pooled?

Talbott No

Burch How accurate are blood-volume measurements under those circumstances?

Talbott I am not sure how accurate they are.

Burch What are the errors due to mixing?

Talbott That is open to considerable question Our only reply and it is a poor answer is that the values were reproducible.

Burch Pooling of blood might possibly produce difficulty Perhaps the so-called circulating blood' volume only is recorded.

Talbott It could be that we were measuring circulating blood volume and nothing more.

Fremont Smith But your plasma protein increase was consistent.

Talbott The hemoconcentration agreed rather well with the decrease in plasma volume.

Burch The quantity of erythrocytes did not change that is, circulating red cells?

Talbott That could best be answered by using radioactive iron.

Barton My memory may be false but I think Smith and Fay (10) had some evidence that the fluid had gone into the tissues, didn t they?

Talbott Yes.

Barton Certainly in animals it has been shown that there is a shift from the blood stream into tissues in these cases but in man I am not sure if I remember the process correctly

Horvath It was indirect evidence based again on Barber s original work. They assumed the same thing

Barton The hemoconcentration would be accepted by most physiologists to indicate that the fluid had gone into the tissues

Crismon Ascites and accumulation of fluid in the thorax, as well as splanchnic pooling have been reported in experimental animals.

Talbott We obtained X rays of our patients immediately before induction and immediately after restoration of body temperature By X ray there was no evidence of any accumulation of fluid in the pleural spaces, nor was there any clinical evidence of abdominal ascites

Barton Though it has not been reported and it does not have enough scientific weight and validity to be reported in the literature, I might mention my slight acquaintance with hypothermia in man. That was in Toronto where they had heard of Talbott s work Psychiatrists there wished to try hypothermia as a form of experimental therapy I was merely concerned as an engineer in providing the cooling cabinet to cool them down. I went over to the Toronto General Hospital, where Dr Richard had done about a dozen terminal cancer cases following the work of Smith and Fay to look at the records, and what struck me at once was this several of the patients had died during the treatment But I looked at the record of blood pressure and in every case where the

patient had died the blood pressure had been maintained well to that point. The patient died a few minutes after they had decided that the temperature was getting too low and had turned off the cooling cabinet and turned on heat. This suggested to me that the answer was that as long as they were kept in the cold state, the blood pressure would be maintained. But they had caused them to have a vasodilatation and—

Fremont Smith They actually turned on heat?

Burton They actually turned on heat.

We did cool one of the psychiatric patients. I had no clinical responsibility I could not have, of course I stayed with him until one in the morning, and the blood pressure had been beautifully maintained.

When I came back the next day I said, "Well, how is he?"

They said Oh, he went flat on us His blood pressure went away down, but he recovered all right

I said What did you do?"

Oh, we took him out of the cabinet and put him into bed with warm blankets.

I pointed out to them that probably that was the reason that his blood pressure had fallen Three weeks later they did the man again, but instead of taking him out of the cabinet they merely turned the cooling off and let him take fifteen to twenty hours to warm up and at no time in that entire period did his blood pressure fall below normal values. My impression is that it did not even fall as much as in your records here.

Fremont Smith In the first case the blood pressure went flat only after they had put him under the hot blankets?

Burton Yes

Fremont Smith They did not put him under the blankets because of blood pressure failure?

Burton No, because they wanted to warm him up

This brings out to me what I think has been proved in animals, and is of great practical importance in the treatment of people with hypothermia the very grave danger of giving them heat, which causes failure in dilatation. Dr Clegborn's experiment (11) done on dogs giving them hemorrhagic shock and leaving them in the cold, indicates that apparently there is no danger of shock from leaving them in the icebox which is comparable to the danger of keeping them in a room at 85 F I think that we should always be aware of the danger in prolonged hypothermia, of a shift of fluid from the blood stream the blood pressure will be maintained as long as there is intense vasoconstriction The very great danger is that before blood volume is adequately increased, vasodilatation will bring about low blood pressure.

Fremont Smith This is of importance with regard to the whole question of shock, and is contrary to the suggestion made earlier because our

whole treatment tends to focus on heating. So it raises the question of whether we might not consider cooling as advantageous for shock, because you have the same vascular phenomenon. You have a reduced blood volume and vasodilatation.

Barton The question has been discussed, and of course the idea that heat might be injurious is a very old one. I think it originated with Dr Barrett in the last war (12). He made the observation that men left out on the battlefield who were not picked up for a couple of days in quite cool weather seemed to fare as well as and even better than, the men that they rushed into overheated shock wards. This set him thinking about it, and he worked out the physiological theory that would indicate what might happen. During the war a great many experiments were done on animals the results of which, I think, seem to point out that there are dangers of heating which are much greater than dangers of letting people be cooled

Fremont Smith That is not therapeutic procedure.

Shumacker Yes. It is recognized that patients in shock are better off left cool than if they are made too warm.

Barton I think Moon's book on shock shows that the dangers of heating in shock are very much greater than the dangers of letting people be cold (13)

Fremont Smith Is application of cold, then, the recognized therapeutic measure?

Barton No. You stop at saying there are very grave dangers of heating. The conventional thing for shock is to give patients much heat, but we now realize that has very grave dangers, and may not be anything like the dangers of letting them be cold

Fremont Smith Is it not quite possible to turn that around? It seems to me that the logical sequence of such a statement is that a certain amount of cold should be applied to patients in shock rather than that we should be afraid of the danger of giving them too much heat. Why don't we find the right temperature to give them, and apply it in a positive way

Horvath There has been experimental work on the use of the cold, not necessarily prophylactic. As far as animals are concerned, experimenters certainly did improve the animals' chances of survival if they kept them cold

Fremont Smith Blalock did that

Horvath And several other people

Fremont Smith What is the status now?

Horvath The Army directive did say it was better to keep patients cool than to overheat them. It was not necessarily followed

Barton As far as this Conference is concerned it isn't a conference on shock, but it is a conference concerned with cases we might find, like that of the Chicago woman, in hypothermia which has been of long hours

duration. I think in that case we ought to be very well aware of this physiology If this shift of fluid has taken place, then we might kill people by applying, as we would naturally do much heat

I was very interested in this problem, and I asked Dr Whillans, the Director of the Medical Division of our Defense Research Board, to find out if there weren t some clinical records in Canada from the hospitals in the North It seemed to me we needed some clinical histories of people found in hypothermia. To our astonishment, we couldn t find a single clinical record of a person found in hypothermia even from the splendid hospitals there

Fremont Smith What about infants?

Burton I think it is a very different physiological problem in infants, as Dr Adolph has shown in young animals I suspect that the answer is that people were dead when they were found, which is frequently the case or if they were still alive, I think most of them probably died before they got into the hospital For them, therefore, there are no records. They died because people did the obvious thing and gave them much heat. But I am just guessing The remarkable fact is that from civilian hospitals we have no clinical records whatever

I have been telling our medical students that this situation is something I hope they will alter if they ever come across a case It would be very valuable to make some observations. We do not even know what the body temperature was, what happened, and so on.

Horvath They did better in the period of 1898 Sharpey-Schafer has a number of very interesting records of actual temperatures of people picked up in snowdrifts and also some notations to the effect that those picked up and not brought immediately to a warm place did better than those brought in and heated.

Burton So I feel the establishment of whether or not the shifting of fluid takes place, as the experiment seemed to indicate, is of tremendous practical importance.

Talbott A simple clinical procedure would be the hemoglobin concentration. If the hematocrit has increased to a significant degree, hypothermia has persisted for a period of time and a decrease in blood volume has occurred If the hematocrit is essentially normal one might be justified in warming at a faster rate.

I would like to have Dr Sellers discuss the effect of diathermy upon vasodilatation. Is it possible with diathermy to restore body temperature without producing a profound vasodilatation of external heat?

Sellers I do not feel able to comment fully on Dr Bigelow s work (14 15) I thought that he might be here However rewarming has been one of his main problems, and he has had the benefit of the advice and practical help of a physicist from the National Research Council on the

design of a suitable diathermy unit that supposedly gives a more uniformly distributed heat than the usual machine does. The machine uses radio frequency As far as I understand, it does not cause any apparent peripheral dilatation. Dr Bigelow seems to feel that its effect is to heat the deep tissues at the same time as it heats the superficial tissues

While I am talking, I might mention two other points that have impressed me in Dr Bigelow's work. As you know his work is chiefly on hypothermia He has used dogs and monkeys, and as the temperature of the body goes down to somewhere around 18 C., I understand that the respiratory function ceases To combat this, he used artificial respiration Then he hit upon the idea of phrenic stimulation and he found that respiration can be maintained very well in hypothermia by stimulating the phrenic nerve. Another or 3 lower — I can't be more precise — and the heart rate, which has been slow sometimes stops altogether He developed an electrical artificial pacemaker for cardiac arrest with application of the electrode directly to the sinoatrial node through the open chest. One of his associates suggested the passing of an intravenous catheter to the sinoatrial node, and placing an electrode in the catheter eliminating the necessity of opening the chest While it is in the region of the node, he has been able to maintain within limits whatever rhythm he wants, and thus decreases the likelihood of sudden cardiovascular collapse He wondered about the effects of these low temperatures below 18° on the psychomotor function As I mentioned last night, he has carried out psychomotor tests on monkeys before and after lowering their temperature to this level As I understand it the monkeys show no deterioration after undergoing such treatment Electroencephalograms show a gradual flattening out of waves which disappear at 18 C then reappear on rewarming

His other work of interest is on hibernation He has used ground hogs and has successfully kept them in true hibernation for a number of months His chemical studies have been fraught with difficulties. One of his projects was to estimate ketosteroid excretion, but the excretion of urine seemed to be so negligible that he wasn't able to measure it

His other chemical studies have been limited, although he intends to continue his work next winter on a larger scale

Barton I think the vital point in these studies which many people are doing on hypothermia is the relation of the time in which the animal has been cold —

Talbott That is very important

Barton — to the efficacy of rapid rewarming I myself feel that the German work at Dachau, even if one put confidence in it which I do not think one should — after all the data might have been invented out of the author's head — does not tell us the answer because all of those

people were warmed up almost as soon as the temperature got to the desired level. A practical case would involve finding someone still alive in the snow who had been there at a low temperature for quite a long while. It may be that once they collapse so to speak, the temperature falls so rapidly that if we find them alive they can t have been there long I should like to see more experiments done on the duration of the period they are kept cold, and how that affects the efficacy of rapid rewarming

Talbott I am in complete agreement, but I wish to make it clear that rapid hypothermia may be of great interest to the Armed Forces, particularly to the Navy and the Air Force. Associated with immersion at sea, there may be a repetition of the Dachau experiment in that the body temperature may fall 10 or 12 F in a short period of time Under such circumstances, the subject probably should be treated by rapid rewarming, not slow rewarming

Horvath Raybom reported resuscitation of some fliers in the North Sea. He had two cases of rapid rewarming against about eight of slow rewarming and the two rapid ones did much better

Burton Isn t the vital point how long they have been cold? If this shift of fluid takes place there may be very grave danger in rapid rewarming

Horvath These were short exposures to the water I think, of twenty to forty minutes duration

Edholm Isn t there perhaps some confusion about terms once more, as to what you mean by rapid rewarming? In the Toronto experiments you described it as rapid rewarming

Burton I don't think I did use the term.

Edholm You said that that was where the danger came in, when they turned on the heat One can say that you have very slow warming up, in which you would allow the patient to return his temperature to normal by his own metabolic efforts, or moderate warming of the kind that you describe or rapid rewarming of the type that was done at Dachau, and that Captain Behnke has done, in which you immerse the subject in hot water at a temperature of 42 to 50 C.

Burton I think we would agree at this point that the intermediate rate of rewarming probably has dangers, and that the choice lies between very slow and very rapid rewarming

Edholm Yes, Moderate reheating I think we can dispose of Wouldn t that be generally accepted?

Siple One consideration that hasn t entered the discussion thus far is the fact that the body thinking of it as a cylinder has a temperature gradient from the inside outward to the shell. As one starts to rewarm, apparently the capillary bed opens up rapidly When this happens, the warm interior blood flowing through this newly opened bed is cooled rather abruptly The circulating blood in turn brings a corresponding sud-

den drop in temperature of the inside core. This is apparent in normal people working out in the cold. They can be out for several hours at a time working at −40 and when they go inside where it is warm, for just a few minutes, for the first time in hours they start to shiver violently and actually begin to feel pain from the cold. It is *after* they have hit the heat, not before, that they notice an abrupt sensation of being colder.

Horvath It is because their temperature keeps on going down. Their rectal temperature goes down still more.

Burton When you start rewarming you do get this extra drop which might possibly carry a patient into a lethal stage.

Siple That is what I thought was in this pattern of rewarming getting a sudden and probably a rather violent drop of a degree or so in internal temperature may be creating some of these phenomena.

Burton What I am trying to emphasize — and I am being a bit vehement about it perhaps — is that we should not decide that there are no grave dangers of rapid rewarming until somebody has done the experiments with different lapses of time after the subjects are cooled before the rewarming.

Talbott And determine the blood volume or some means whereby an index is available as to whether or not one would be in trouble if the body temperature were restored rapidly.

Burton If you left them two or three hours before they were cold would it then be safe to use the very rapid rewarming?

Shumacker Are there any data on the rapidity with which one gets maximal concentration of hemoglobin?

Talbott In our studies the maximum concentration of hemoglobin did not appear until twelve or fifteen hours after beginning induction. Therefore, I believe that rapid induction is quite a different mechanism, or produces different changes internally than slow induction does.

Horvath May I ask just one more question about Dr. Bigelow's experiments? I am curious about this use of the high-frequency current. Ordinarily at least in our clinical experience, although we heat the deep tissues, and can elevate the deep tissue temperature 2 or 4 C, we also heat the superficial tissues. They may show an elevation up to 9 or 10 C. I was just wondering whether Dr. Bigelow had been doing this heating in the cold so as to keep the peripheral tissues constricted relatively speaking, and to drive most of the heat that was induced deep or whatever he might be changing in the deep tissues, and not influencing the superficial tissues.

Sellers When I was speaking before I did not mean to give the impression, if I did, that the superficial tissues were not heated because certainly what you say is correct. Bigelow increases the general temperature very rapidly and perhaps Dr. Burton could comment on the physics, but

I understand that it is a very high radio-frequency machine that he is using (14)

Horvath Is it in meters?

Sellers It minimizes the differential between deep and superficial temperature but, of course, speed is the big point, and there is bound to be some dilatation of the superficial investigations as well.

Shumacker Do you know whether his animals show hemoconcentration at this time?

Sellers I am afraid I would be guessing

Shumacker But you do know that they are relatively short-term experiments, do you not?

Sellers Yes I think he usually keeps them cold for about five hours, or something like that

Burton I wouldn t want to appear an opponent of the rapid rewarming I think it is quite likely that even if the animal has been cold a long while rapid rewarming is still effective, but I am trying to encourage someone to do these experiments in such a manner as to find out whether the length of time in which animals are cold does affect the efficacy of rapid rewarming Until we know that, I do not think I would like to say that rapid rewarming is without danger

Behnke It is certainly obvious that it is necessary to prevent blood from the core from passing through the cold periphery isn't it?

Burton Are you thinking of the other danger of this when you start rewarming, you always get a deep core drop and that might carry them to a lethal temperature?

Behnke The very important physiological principle can be emphasized from cold-water experiments and rewarming, that there are two circulations the core and the periphery One can isolate the periphery by cold and maintain an organism in very good condition for a long period of time with a circulation only through the core and certainly at temperatures at 90 F and above, one has a very efficient organism in which blood is flowing through the core and not through the periphery This principle certainly seems to be applicable in shock, in burns, and in those states in which the periphery is injured, namely to limit circulation through the periphery and to limit absorption of toxins and other materials, and to improve the state of the organism by confining the circulating blood to a smaller area. I think this is brought out in cold experiments. It is seen, for example, in a slowing of the pulse rate. Oxygen consumption may be increased sixfold because of shivering but the pulse rate which would ordinarily be 140 with comparable exercise on a bicycle, is only 88. This indicates very efficient heart action.

Now Dr Burton s suggestion as to the type of experimental work to be carried out is important, but I wonder if it is the shift of fluid volume

that it is as important as the action of the heart itself Above 90 F I believe one has a heart that is functioning well. Now below 90 cardiac function may be impaired Certainly one can withdraw a pint or even a quart of blood from an individual without causing him too much trouble, so it may not be due so much to the fluid volume as it is to the condition of the heart.

In these patients, Dr Talbott, in which prolonged hypothermia was carried out, what was the condition of the heart in terms of rhythm?

Talbott The changes in cardiac rhythm were invariably present below 80 F and sometimes when the internal temperature was no lower than 85 F I do not recall any arrhythmias appearing with internal temperatures at 90 or above.

Behnke 90 F.?

Talbott The heart appeared to be acting normally if the internal temperature were no lower than 90 F There were at least two potential hazards below 90 F Cardiac dysfunction was one. The other was the possibility of shock appearing with rapid rewarming Shock could be induced with return of body temperature to normal in the 90 s as well as in the 80 s.

Behnke How did you warm the patient rapidly by hot water?

Talbott The patient was not warmed rapidly His temperature was merely permitted to rise In each instance the source of cold was removed, and restorative processes were allowed to operate

Behnke That isn t rapid rewarming, perhaps.

Talbott You are correct It is faster rewarming than we felt desirable, because when we start from a temperature at 80 and go up to 98 F we prefer twelve hours to accomplish this. We kept the cold machine on intermittently for this long period of time rather than shut the machine off and let the patient s temperature return to normal within a few hours.

Behnke The type of experiment that I should like to see done in addition to that suggested by Dr Burton, is one in which, by means of diathermy the normal temperature of the heart, liver and other organs is maintained and the periphery kept cold.

Horvath In man, you just can t heat the heart by diathermy you can t get enough temperature down into the heart region to change the heart temperature.

Crismon We have made an approach to that in rats by putting a resistance coil in a catheter down the esophagus to heart level, and by supplying heat directly by that means, while the rest of the animal was cold (16) Under those circumstances the electrocardiogram reverts to a normal pattern where previously it had no waves at all, and prolonged QRS complexes. The arterial pressure rises and respiration increases. Core temperature, as far as we were able to measure, does not come up at all. That

would mean the change of only a few tenths of a degree in the temperature of the pacemaker to accomplish that. I think it is important to stress the two phases of the mechanism of circulatory collapse in hypothermia. In one circumstance we deal with problems owing to failure of venous return. It may be that absence of shivering is responsible, or perhaps the longer phase of removal of fluid. In the colder temperatures the heart *itself begins to change its pattern of function so that a longer time is used* in the isometric contraction phase and a smaller span of time is used in the ejection phase. Therefore, the stroke volume goes down, leaving a tremendous systolic remainder That was demonstrated on experimental animals Wiggers showed that a long time ago (17)

Conn I think there is another experiment, in addition to the one that Dr Behnke has just brought up that might throw a little light on the subject If peripheral vasoconstriction could be maintained, then during the application of rapid rewarming both the peripheral vasodilatation and the drop in internal temperature that occurs from it would be prevented

If one were to administer nor-epinephrine intravenously as a drip, and then apply rapid rewarming, is it not likely that warming would be much more gradual because of the absence of peripheral vasodilatation, and might not one in this way also prevent the vascular collapse?

Talbott Are you presuming that there is cardiac failure?

Crismon Not in the subjects that are cooled only to the extent that yours were but in the experimental animals that had been taken at much lower temperatures.

Talbott There must be cardiac failure.

Crismon There is.

Burton I think Hegnauer has something on this that the terminal event is ventricular fibrillation (18)

Horvath That is induced by placing the catheter in the ventricle. He is going to publish a paper showing that that is actually what happened. that the ventricular fibrillation is set up by the catheter itself that he does get arrhythmias of various sorts, and that there is apparently an alteration in conduction time.

Burton It is a conduction breakdown (19)

Minard Mr Chairman in one of Bigelow s reports (15) he feels that cardiac failure is one of the terminal events and this is preceded by a marked rise in venous pressure.

Talbott This is not a low temperature range?

Minard In the temperature range between 20 and 15 C. By venesection he could restore cardiac function in some cases, and following venesection, if he rapidly rewarmed the animal, he frequently achieved complete recovery Without this procedure, the animal usually went into ventricular fibrillation.

Talbott Again we must define our experimental limits Bigelow's experiments were of only two or three hours duration

Siple Right.

Minard That, I believe, is correct. You mean there was not the fluid shift about which we have been talking?

Talbott Yes.

Gottschalk Is this a peripheral venous pressure or central venous pressure?

Minard Central. I believe he measured it by catheter

Edholm Did you think there was a continued fall in blood volume with hypothermia?

Talbott It may take as long as twelve hours to reach a minimum temperature. We did not reach this within a space of four hours

Shumacker What happens to the lost fluid after they are rewarmed?

Talbott In our experiments we proceeded uphill at approximately the same speed as that with which we descended hoping that we would restore the blood volume at the same rate that it was lost

Schumacker Did it?

Talbott There was clinical evidence that we got into little trouble when we proceeded slowly in contrast to rapid rewarming. One may encounter difficulty anywhere along the line on the way back to normal if the process is too rapid. In such circumstances the patient may be in shock and should be treated by cooling and later by permitting the temperature to return to normal

Behnke What is the degree of hemoconcentration

Talbott It may be as great as 25 to 30 per cent.

Behnke One should consider with reference to fluid shifts, that sweating on a hot day may result in a loss of 5 or 6 liters of fluid. Can one get excited over a shift of say —

Talbott The loss of fluid in the sweat is primarily extracellular The hemoconcentration of 25 or 30 per cent implied a reduction in plasma volume of this magnitude This is quite different in general dehydration which accompanies exposure to warm weather

Edholm Is it possible that there is another difference in the hypothermia induced by your methods, Dr Talbott or in that of the woman in the snow bank, and of those immersed in cold water? I was thinking of the hydrostatic effect on the circulation in the water and the removal of that hydrostatic effect when subjects are removed from the water

Talbott One of the patients described by Wayburn died some time after rescue (20) The patient was alive on rescue but did not survive hospitalization.

Edholm That is what I really had in mind It isn't only the matter of rewarming after you come out of the water It is a question that if you are being rewarmed by being put straight into a bath you are once more sup-

porting the circulation physically It may be that that factor is of importance in immersion hypothermia as opposed to hypothermia in air

Crismon The very cold ones do better if you bleed them. The thing you suggest would tend to raise the venous return.

Edholm That is in the stage of cardiac failure.

Talbott Cardiac failure is a good probability when the core temperature is 10 or 15 below normal

Burton Wasn t there an RAF case where a man was rescued from the sea and actually climbed out of the boat and walked out to the beach and collapsed and died?

Talbott One of the reports from the Armed Forces is similar The patient appeared to be alive and mentally alert but died shortly after

Behnke It is believed that a number of patients — not a few but quite a number — have been lost by taking them out of the cold water Specifically if the water temperature is 70 F an individual s deep body temperature may fall, let s say 4 F in one hour On the other hand, if he is brought into the air at 80 F during the next twenty minutes the temperature may fall 6 F If he has been in water long enough so that the core temperature falls to 88 F or 85 F and is then brought out into the comparatively warm air environment, the subsequent additional drop in temperature may be such as to interfere with heart action

Burch I should like to ask a question. Have you given any thought to the mechanism by which this fluid escapes through the vessels?

Talbott No good ideas as to the mechanism.

Burch You don t think it is entirely hydrostatic, do you?

Talbott No I presume the patients were in a supine position as our experiments were.

Siple Hydrostatic from increased pressures to start with. Is that possible?

Burton I am astonished that nobody has mentioned the use of cortisone. Surely it can t be that nobody has tried cortisone?

Kark The patient at Michael Reese was given cortisone as far as I remember I read about it in a newspaper!

Talbott Although the doctor caring for the patient initially thought there was some benefit from cortisone I believe subsequently that no particular benefit was attributed to this drug

Siple I think we can divide the externally induced hypothermia into at least three different categories, in which the effects that we have been discussing may have a different approach or different end result. The first one is the total drop such as the experiments wherein you brought the whole body down, but at moderate temperatures that is, you brought the body temperatures down, still not at freezing and gradually dropped the whole organism. The second one is the peripheral drop in which you

have an extremely low temperature, in which you would have a strong temperature gradient between the interior and exterior There would be a similarity between those two in that the body temperature would eventually drop down below you have a very sharp gradient and if it is sharp enough you may freeze the exterior The third one from a cold-injury standpoint, is extremely important hypothermia over a long period of time for extremities in which the whole body temperature still stays up that is, which leads into the trench foot pattern, in which you have a hyperthermia of a portion of the body with perhaps a slight drop through the whole body It is still holding it above a freezing temperature, but holding it down for a long period of time That timing aspect is extremely essential in considering this whole trench-foot picture

Sellers An example of that last case is seen in our rats that are exposed to a temperature just above freezing They almost invariably lose their ears, and in many cases lose their tails after a varying period of time that may be anywhere from a week or so up to twelve or fifteen months

Siple As I understand the general picture it is that with the reduction of the circulation for a sufficient period of time there was an anoxic effect which apparently caused some destruction of tissue We have looked at this problem from various angles but in my opinion it is a question of timing It is obvious from the practical side that general exposure to cold and general wetness induces trench foot Immersion damage seems to occur a little faster than exposure causing trench foot on land in cold conditions. Generally it seems to take from twenty four to thirty-six or even seventy-two hours before the bad cases appear Holding the extremities in constriction for a long period of time apparently is an important link in the chain of events that creates the injury The question is Where is the safe time limitation for remaining in constriction? Our bodies obviously use constriction in the extremities to advantage for short-duration exposure, but it becomes lethal to those parts if it is held for any great length of time.

Talbott I think we might interrupt this discussion on hypothermia to have Dr Edholm tell us about some of his work, or he may report on experimental work going on in his country if he would like to do so

Edholm I should like to emphasize that the work that is going on in my own laboratory is all in a very preliminary stage and I do not think, therefore, too much importance should be paid to anything that we can say except from the point of view of discussion

I described briefly yesterday some of the work on local effect of cold, or rather I should say local effect of cold water on the hand in which there is very marked vasodilatation occurring with or without hunting Now we have only maintained such experiments for periods of not more than an hour to an hour and a half So we can t say very much about the rela

tionship of such experiments to immersion foot or immersion hand. If you have a hand in water ranging from 0° to 5° C. for an hour to an hour and a half you don't have anything apparently very much in the way of aftereffects in that hand. The hand volume is increased somewhat if it is in a dependent position but if you maintain the hand either at or about heart level there is no change in hand volume. The temperature within that hand is probably maintained fairly high owing to the very rapid blood flow. I think an important problem to work out in relationship to the immersion syndrome, will be the stage at which one is getting changes that are going to lead on to damage afterward.

It seems to me a little difficult to attempt to ascribe all the changes purely to anoxia, because certainly at any rate over these short periods of time one maintains an increased blood flow in cold water.

It may be that after that preliminary hour to an hour and a half with further immersion the blood flow comes down again but so far we have not got any evidence of that.

Siple: Is that in the periphery?

Edholm: In the hand.

Siple: Would it be out into the extremity of the fingers, or would it be deep in the hand?

Edholm: No. The greatest degree of dilatation is in the terminal portion of the fingers and then it decreases as you come up into the hand itself but even in the hand you have an increased blood flow, a very considerably increased blood flow.

There are one or two aspects of this which are of some interest, that is, the very great heat loss that you can have from one hand alone in cold water. These experiments have been carried out in the laboratory at room temperature of a range of from 18° to 20° C. wearing ordinary clothing such as is worn in England. You can lose up to thirty, even forty large calories from one hand alone in an hour which, of course, is a very considerable heat loss.

There are some curious things about the sensations of cold which have already been referred to in other respects. When you have your hand in ice water you do not feel cold generally even though there is a drop in rectal temperature and in mouth temperature. When your hand comes out of the cold water within quite a short period of time, say five to ten minutes, you feel intense cold and you get generalized goose flesh. I personally find that rather hard to understand. It is certainly not due to, or I think not very largely due to an increased return of cold blood from the cooled part, because you have this increased blood flow going on through the part during the whole period of the experiment, and the blood of course, is returning from that hand at a low temperature. We have made some temperature measurements over the veins in the fore-

arm, and they show temperatures of the order of 18° to 20° the skin in between being of the order of 26° to 28° C., so that there is cold blood coming back during the experiment. But you do not feel cold during the period in which the hand is immersed.

Allen. Can this be modified by venous occlusion? Have you tried that?

Edholm. We have been doing plethysmograph studies, as well as calorimeter studies, with venous occlusion on the wrist and on the upper forearm, but we have never maintained that occlusion for more than about five minutes. If you put on an arterial occlusion, you cannot maintain that for more than about five or six minutes because of the pain, which is intense.

We have been interested in the effects of cold on the venous circulation. It is extremely difficult to get a satisfactory blood-flow record in the cold vasodilatated state using a plethysmograph. When venous occlusion is applied, there is an immediate rise in volume for perhaps one pulse beat only and then the volume record flattens off. This implies that the venous reservoir is very small or very inelastic.

Professor Sharpey Schafer has some unpublished pressure records taken from veins draining a cold vasodilatated finger which show very marked venous pulsation.

We have also been interested in what might be termed the Bazett phenomenon. Dr Bazett postulated that in the cold, the venous return is by way of the venae comites and not the superficial veins.

We haven't been able to work out by any means satisfactorily the proportion of blood coming back by way of the superficial and deep veins. I think we can say that under these rather special conditions of local cooling of one hand, there is a considerable volume of blood returning by the superficial veins. I say that because the veins are prominent in the forearm.

The gradient of temperature along these superficial veins of the forearm draining from the hand is quite flat from the wrist up to the bend of the elbow at the junction with the deep vein of the forearm. At this point along a distance of some 2 cm. there is a rise of 5° to 6° C. which suggests that there is a considerable blood flow from the deep veins at the junction of the basilic and cephalic veins.

Blood-flow determinations have also been made in the forearm at the time when the hand is in cold water. When a venous occlusion is applied at the wrist, the hand volume increases only for one or two pulse beats. We thought we would then detect the increased venous flow from the hand in the forearm plethysmograph record. Well, we have no good evidence that we do pick up that leak-through unless it is occurring extremely quickly. What we can say so far as our records may be valid, is that the blood flow in the forearm is not reduced by immersing the hand in cold water.

We have also tried cooling the forearm alone, and there again we have done very few experiments, but such as we have done suggest that there may be some increase in blood flow in the forearm also at low temperatures, although this effect is not as dramatic as that occurring in the finger or in the hand But again I do not think that our data are sufficient for us to be confident.

The other effect of local cold on which we have a few observations is on blood-pressure changes. When the hand is immersed in ice water there is a rise of blood pressure within the first minute or so a rise chiefly in systolic pressure, with a small rise in diastolic pressure. The pressure may then fall slightly if the experiment is continued the systolic pressure climbs a little but not very much more, whereas the diastolic pressure continues to rise. During this slow continued rise there is no pain in the hand. The pain is an immediate phenomenon which lasts for not more than five minutes and perhaps a good deal less, depending upon the time the vasodilatation develops. But in spite of the lack of pain with this continued cold immersion of the hand the diastolic pressure continues to rise, and at the end of an hour diastolic pressure readings might be over 115 mm.Hg the initial level being 75 mm.Hg

I do not know what relationship this may have to the initial rise of blood pressure that you are reporting Dr Talbott, with your general hypothermia, but I think, judging from your graphs, there was no very great rise in diastolic pressure

Talbott No I think the pulse pressure varied only slightly Changes were observed in the same direction in the systolic and diastolic phase.

Barton Do you think this could be an adrenal effect, this steady rise?

Edholm Dr Pugh, in my laboratory has done a few studies on eosinophil counts If there is no pain, there is no fall in the eosinophils with this kind of immersion. As far as that goes there is not much evidence of adrenal activity I do not think we can really say anything about that.

Burch Does the fall of eosinophils occur only from an endocrine factor?

Edholm You have raised a very fundamental point. So far we have been using eosinophils as an empirical index. We do not know their function or where they go to we do not know if they are destroyed or if they are stored, so the use of eosinophils is by no means on a firm basis.

Burch Dr Conn might know

Conn I think one should be aware of the limitations of the eosinophil count as an index of adrenocortical activity When he does keep in mind the limitations, he may be able to use eosinophil counts to great advantage. It has been demonstrated that an injection of epinephrine in totally adrenalectomized animals will cause a fall in eosinophils, and George Thorn and others have recently reported cases of Addison's disease that

have had a sharp fall of eosinophils with epinephrine but not with ACTH. Dr C. N H. Long and his group have discovered that the eosinopenia following epinephrine in adrenalectomized male rats is abolished by castration, and suggest the possibility that adrenal cell rests in the testes may respond to the endogenous ACTH released by epinephrine Until some of the basic problems connected with the mechanisms of eosinopenia and the fate of the cells themselves have been clarified it would seem wise not to regard eosinopenia in man as a specific indicator of increased adrenocortical function

Shumacker Is the normal difference between oxygen saturation of arterial and venous blood abolished or diminished in the hand during cooling, Dr Edholm?

Edholm I am afraid we haven t any studies on that as yet

Siple On your experiments that you have been describing in these cases, was just the hand or just the forearm exposed to the cold?

Edholm Yes.

Siple What is the ambient condition of exposure for the body as a whole?

Edholm The room temperature has been in the range of 18 to 20 C the subjects wearing ordinary clothes otherwise, in generally comfortable conditions

Siple Have you done any experiments where you have had the body in a relatively chilled state to start with? If so is this same phenomenon of increased blood flow as pronounced?

Edholm If you have your subject cold — and this has been done not by ourselves but by Greenfield — you still have a local vasodilatation in the hand immersed in cold water (21 22, 23) That vasodilatation is reduced, but there is still an increased flow

The subject sat with his trunk and legs bare at a room temperature of 13 to 16° C., with two or three electric fans playing on him He was cold before his hand was put into the calorimeter There was nevertheless an increase in blood flow although it was much less than when he was comfortably warm.

Siple What was the temperature of the water?

Edholm It ranged from 0 C. to 5 C

Siple Have you ever tried the experiment by starting with comfortable water temperatures and bringing the temperature down very slowly to see whether that same tendency for dilatation occurs?

Edholm We have only done a certain number of experiments in which we have kept the hand and arm in water at 12 C. up to eight hours. Under these conditions there is a very small blood flow indeed through both hand and forearm. There is no vasodilatation under these conditions whatsoever

We have also tried cooling the forearm alone, and there again we have done very few experiments, but such as we have done suggest that there may be some increase in blood flow in the forearm also at low temperatures, although this effect is not as dramatic as that occurring in the finger or in the hand. But again I do not think that our data are sufficient for us to be confident.

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Siple: Have you ever tried the experiment by starting with comfortable water temperatures and bringing the temperature down very slowly to see whether that same tendency for dilatation occurs?

Edholm: We have only done a certain number of experiments in which we have kept the hand and arm in water at 12° C. up to eight hours. Under these conditions there is a very small blood flow indeed through both hand and forearm. There is no vasodilatation under these conditions whatsoever.

We have also tried cooling the forearm alone, and there again we have done very few experiments, but such as we have done suggest that there may be some increase in blood flow in the forearm also at low temperatures, although this effect is not as dramatic as that occurring in the finger or in the hand. But again I do not think that our data are sufficient for us to be confident.

The other effect of local cold on which we have a few observations is on blood-pressure changes When the hand is immersed in ice water, there is a rise of blood pressure within the first minute or so, a rise chiefly in systolic pressure, with a small rise in diastolic pressure. The pressure may then fall slightly if the experiment is continued the systolic pressure climbs a little but not very much more, whereas the diastolic pressure continues to rise. During this slow continued rise there is no pain in the hand. The pain is an immediate phenomenon which lasts for not more than five minutes and perhaps a good deal less, depending upon the time the vasodilatation develops But in spite of the lack of pain with this continued cold immersion of the hand, the diastolic pressure continues to rise, and at the end of an hour diastolic pressure readings might be over 115 mm.Hg the initial level being 75 mm.Hg

I do not know what relationship this may have to the initial rise of blood pressure that you are reporting Dr. Talbott, with your general hypothermia, but I think, judging from your graphs, there was no very great rise in diastolic pressure

Talbott No I think the pulse pressure varied only slightly Changes were observed in the same direction in the systolic and diastolic phase.

Barton Do you think this could be an adrenal effect, this steady rise?

Edholm Dr Pugh, in my laboratory has done a few studies on eosinophil counts. If there is no pain, there is no fall in the eosinophils with this kind of immersion. As far as that goes, there is not much evidence of adrenal activity I do not think we can really say anything about that.

Burch Does the fall of eosinophils occur only from an endocrine factor?

Edholm You have raised a very fundamental point. So far we have been using eosinophils as an empirical index. We do not know their function or where they go to we do not know if they are destroyed or if they are stored, so the use of eosinophils is by no means on a firm basis.

Burch Dr Conn might know

Conn I think one should be aware of the limitations of the eosinophil count as an index of adrenocortical activity When he does keep in mind the limitations, he may be able to use eosinophil counts to great advantage. It has been demonstrated that an injection of epinephrine in totally adrenalectomized animals will cause a fall in eosinophils, and George Thorn and others have recently reported cases of Addison's disease that

have had a sharp fall of eosinophils with epinephrine but not with ACTH. Dr C. N. H. Long and his group have discovered that the eosinopenia following epinephrine in adrenalectomized male rats is abolished by castration, and suggest the possibility that adrenal cell rests in the testes may respond to the endogenous ACTH released by epinephrine. Until some of the basic problems connected with the mechanisms of eosinopenia and the fate of the cells themselves have been clarified it would seem wise not to regard eosinopenia in man as a specific indicator of increased adrenocortical function.

Shumacker Is the normal difference between oxygen saturation of arterial and venous blood abolished or diminished in the hand during cooling, Dr Edholm?

Edholm I am afraid we haven t any studies on that as yet

Siple On your experiments that you have been describing in these cases, was just the hand or just the forearm exposed to the cold?

Edholm Yes.

Siple What is the ambient condition of exposure for the body as a whole?

Edholm The room temperature has been in the range of 18 to 20 C. the subjects wearing ordinary clothes otherwise, in generally comfortable conditions.

Siple Have you done any experiments where you have had the body in a relatively chilled state to start with? If so is this same phenomenon of increased blood flow as pronounced?

Edholm If you have your subject cold — and this has been done not by ourselves but by Greenfield — you still have a local vasodilatation in the hand immersed in cold water (21 22 23) That vasodilatation is reduced, but there is still an increased flow

The subject sat with his trunk and legs bare, at a room temperature of 13 to 16 C., with two or three electric fans playing on him. He was cold before his hand was put into the calorimeter There was nevertheless an increase in blood flow although it was much less than when he was comfortably warm.

Siple What was the temperature of the water?

Edholm It ranged from 0 C. to 5 C.

Siple Have you ever tried the experiment by starting with comfortable water temperatures and bringing the temperature down very slowly to see whether that same tendency for dilatation occurs?

Edholm We have only done a certain number of experiments in which we have kept the hand and arm in water at 12 C. up to eight hours. Under these conditions there is a very small blood flow indeed through both hand and forearm. There is no vasodilatation under these conditions whatsoever

Siple The thing that I was driving at with this question was my feeling that you are dealing with a stimulus that creates dilatation which is not necessarily akin to the constriction phenomenon that is observed generally in slow or gradual cooling In such cases you would expect long-lasting constriction, as in trench-foot exposure.

You have made a very important observation in showing that with a strong stimulus you do get a dilatation in the extremities We know for example, that the head reacts normally to a cold stimulus, by dilatation. Even though one does not cover up his head in moderately cold and not too windy weather he may still feel comfortable. People believe that if their hands and feet were like their head they would be perfectly comfortable in cold weather They fail to realize the disproportionate amount of body heat loss from the head as compared to that lost from the feet and hands. More and more blood keeps flowing to the head to try to make up for the increased cold exposure It would indicate at least that there is something that controls the flow of blood locally in the hand, and that the constrictors and dilators for the whole system (arm and hand) are some place in a center above the hand

Behnke Do you get a horseshoe curve? I refer to what Sir Thomas Lewis showed a long time ago that minimal blood flow in the hand occurs around 15 to 20 C., and then the blood flow Dr Edbolm, at 0 to 5 C. is about the same as that observed at 38 C.

Edholm Or even higher

Behnke Yes even higher That is the amazing thing Isn t it quite important to determine the minimal blood flow level, and then may you not interpret the augmented blood flow at a lower temperature, say below 12 or 15 C., as the first indication of some type of injury?

Edholm I think that is the point. Is it injury response? Certainly as Greenfield showed it is not dependent on the vasomotor system. It is a local response, and presumably involves a humoral mechanism, but I do not think that we have any evidence as to what that mechanism may be.

Horvath Don t you show cycles which get progressively smaller and smaller?

Edholm Not under the conditions we have employed.

Siple Does fatigue occur during the experiment?

Edholm We have gone on for only a maximum of an hour and a half and during that period there is marked variation from subject to subject in the degree of constriction which occurs during that period. You may have very little hunting during that time you may have very marked hunting occurring But there is no evidence, I think, from any of our records so far that there is any fatigue.

Burton I am thinking of a possible mechanism of this which would be almost purely mechanical. Have you thought of what happens if you wait

until he has his dilatation, and then suddenly while the hand is in dilatation, put it back into tepid water? What happens to the dilatation then? Does it disappear and go back to a moderately low flow?

Edholm We have done that experiment without measuring the flow because we have been interested in the pain produced by cold. Perhaps others have some information or have done the experiments, but the pain with cold is very curious When your hand goes immediately into the ice water the pain is extremely unpleasant there may even be syncope. That pain passes off as the vasodilatation comes on. Your hand may be in for an hour and a half I am not going to say it is perfectly comfortable, but there is not very much pain after the initial episode. There is some slight discomfort, and that is all except during periods of constriction. Now take that hand out and put it in tepid water of 30 and you have intense pain.

Barton You have to put it into a tepid calorimeter

Edholm We have not done that.

Barton If this mechanism that I have postulated in my mind is true, you should get a decrease when you put it in tepid water

Behnke Is there an anesthesia of the sensory endings, and is it possible that one does not feel cold because of the anesthesia?

Edholm In the period of an hour and a half there may be some but there is nothing very dramatic in the way of sensory loss. You have loss of finger dexterity of course, but not very great, not as great, for instance, as when muscles of the forearm are cooled, when the fingers can scarcely be moved at all But I do not think there can be any great anesthesia, because if during this immersion there is vasoconstriction, you will get pain.

Behnke Have you tried the pinprick test?

Edholm Yes.

Behnke Does one feel as much pain with the hand in cold water?

Edholm I wouldn t like to say that there is no loss of sensation I think there may be some loss of sensation.

Behnke This is not the reason why one does not feel pain?

Edholm I do not think so.

Behnke It is not due to anesthesia?

Edholm No

Barton You still feel t at the demarcation point at the wrist?

Edholm No, not very clearly possibly slightly

Barton Isn t it true that when you immerse in cold water the pain is all around where the body enters the water?

Behnke Yes, it seemed to be but the pain in the cold water test, when the whole body is immersed, is greater when the hands are under water Presumably we did not keep our hands under water long enough. If we could keep our hands under water perhaps the pain would go away but

the only pain one felt really was the extremely painful sensation in the toes and feet during the whole period. This pain did not disappear during the period of exposure (about one hour)

Edholm There is no doubt whatever that this local response is markedly affected by the general state of body temperature

Mowrey I should like to ask Dr Shumacker in refrigeration anesthesia used in diabetic gangrene, how long does it take before the pain in the extremity disappears after packing in ice?

Shumacker I cannot answer the question in a precise way I do not use refrigeration anesthesia for operative procedures, but only use local refrigeration in order to achieve a physiological amputation of an infected limb which has to be amputated surgically later on. In such circumstances the relief of pain is quite prompt, but I do not know precisely how long it takes. When the ice is first applied, and especially if a tight tourniquet is applied at the same time, as is often the case, there may be some transient pain at first. For this reason we often give some sedation beforehand. Shortly after application of the ice boot, the limb becomes quite comfortable.

Mowrey It is within the period of an hour?

Shumacker Yes

Talbott Within fifteen minutes

Shumacker I would say somewhere between five or ten minutes and an hour

Behnke Dr Edholm, I think that it is very important to make studies of the degree of saturation of the hemoglobin. One may get arterialized blood from the veins during exposure of the hand in hot water It would be very interesting if beginning with a minimal blood flow say at 15 or 20 C. there was a correlation between the increased blood flow when the temperature was subsequently lowered and the lessened degree of desaturation of the blood.

Dr Horvath, at what temperature is there an appreciable reduction of oxygen saturation of the hemoglobin?

Horvath It starts right away It goes down and becomes progressively worse.

Behnke What kind of curve does one get? I have not seen it published, by the way Has it been published?

Horvath Oh, yes I think in 1942 or 1941

Talbott What was the question?

Horvath That oxygen curve

Talbott That was in the *American Journal of Physiology* (8)

Horvath There is also to be published a rather extensive series by Penrod on various temperatures, but at present not enough has been published to indicate whether it is linear or not.

Burton At 20 C. it only takes 10 mm. of oxygen tension to saturate blood. There is a very marked decrease indeed.

Behnke Could the increase in circulation be a response to anoxia?

Edholm The oxygen consumption of the hand is very big

Burch When submerging the hand, did you submerge only the hand and leave the fingertips out of the water?

Edholm No we put in either one finger or the whole hand.

Burch You did not do the experiment of Lewis in his study of Raynaud's disease, in which he left the fingertips out of the cool water?

Edholm No Wolff and Pochin recently reported some observations on the after response to cold (24)

Siple In accordance with the idea of bringing the temperature down very gradually instead of creating anomalous sharp, local stimulus, and recalling the horseshoe curve Dr Behnke described a while ago I think it would be extremely important to find out if this holds true for the constriction and subsequent dilatation. One of the things that we note in the sequence of events leading to trench-foot injury is the failure of a warning that the body is in danger It is one of the few thermal conditions of potential hazard where the warning disappears upon exposure to low temperature. Apparently the temperature gradient through the skin ordinarily activates the pain. For example, in the case of immersed hands starting with a comfortable water temperature, if the temperature were lowered very gradually only a fraction of a degree at a time, one would assume that because of a lack of sharp thermal gradient in the skin the temperature could pass right on through the level where pain should appear but without experiencing it actually Under such circumstances I wonder whether the type of dilatation will appear or not appear? I think that that may be rather important, because, for example, under dry winter Arctic conditions, trench foot is virtually never important I have assumed that if a man had pain it warned him, and he took care of himself or that he went on if he had to and got frozen, but that he never got trench foot. Where one gradually coasts down, without any warning, and never even gets to freezing, one is not necessarily very uncomfortable and therefore, is able to stay in the danger zone for so long a time that one may get into trouble. If any of you could coast that far down and see whether or not the dilatation will actually happen at a physically low temperature, or if you could find that it was due to lack of pain stimulus that had worn itself out and had come to an end, then you could see whether the skin had gotten cold enough to stop the pain flow

Edholm I think I can answer part of that it does not appear to be due to the pain stimulus, because it does occur in subjects with complete de nervation of the hand or finger

Siple Then you would predict that in this experiment, after the tem-

perature had gotten down to a certain point the dilatation would actually occur?

Edholm Well, I think I had better do the experiment.

There is only one other piece of work that would be worth while reporting here. It is quite a different subject. Dr Hatfield in my department has been determining again the thermal conductance of human tissue (25) He has measured thermal conductance in fat and in muscle. The figures he has are very different from those which one obtains with beef muscle and beef fat. Some time ago Hardy and Soderstrom, discussing the peripheral blood flow in subjects exposed to various temperatures, used a figure for the thermal conductance of the superficial tissues which was based in part upon measurements of the conductance of beef fat and muscle, which they found to be almost identical Human fat and human muscle do not have an identical conductance human muscle conducts about two or three times better than human fat does. Hatfield also estimated the conductance of beef fat and beef muscle and obtained the same figures that Hardy and Soderstrom obtained (26)

Dr Talbott mentioned that in one of his hypothermia experiments the buttocks became rock hard.

It is reported in the literature that the solidification points of fat vary a good deal in different animals, but human fat solidifies at about 15 C so one presumably would expect to feel solid fat at temperatures below 15 C. I wonder if the explanation of your observation is that the fat had solidified, and if a similar explanation would account for the hardness of the face when it is apparently frostbitten.

Burton Have any studies been made of fat for different parts of the body? I am thinking of the experiments on the caribou the solidification point with fat from the hand might be very different with fat from the abdomen.

Edholm We are hoping to do that. It is not very easy to get a very satisfactory end point in these so-called solidification measurements.

Kark Melting point of fat is that what you are doing?

Edholm If you like, melting point, or the solidification point.

Kark What about using iodine-numbers degree of saturation, which apparently is also related to this ease of solidification?

Edholm There are figures in the literature showing a very considerable difference in different species but I do not think they have been done from that point of view

Burton It would be nice to do the experiments done on the caribou on the human.

Kark There is a man in Norway named Schmidt Nielsen (27) who showed that the lower the skin temperature of a man s body the lower the melting point of the peripheral fat. I wondered whether you had

done any measurements of heat conduction through human fat in summer and in winter? I think that would be very interesting to know about.

Edholm We haven t any such evidence.

Allen Have you done any studies along the line of those which you have reported, in which you have blocked the autonomic nervous system with drugs such as tetraethyl or C_6 or perhaps cervical thoracic block with cocaine, and so on?

Edholm Dr Greenfield has blocked the peripheral nerves and still obtains vasodilatation in the cold.

Allen So it seems quite clearly a local effect. I think it is pretty certain to be a local effect, although it may be modified by the vasomotor.

Behnke Is the temperature of the returning venous blood lower after the hand is withdrawn from the water?

Edholm No it doesn t seem to drop any further

Barcb Do you differentiate skin blood flow from muscle flow in the values of vasodilatation presented?

Edholm We have only examined the hand by itself the finger by itself, and the forearm The forearm studies need to be done very much more thoroughly The finger certainly has the highest flow then the hand. I think we can fairly say that the forearm does not appear to show this very marked vasodilatation, although there may be a slight dilatation.

I do not know of anyone who has any information about what may be an early injury phenomenon. I do not know whether Captain Behnke had any signs of injury in the skin after his immersion experiments?

Behnk No Injury is limited to the toes, a little paresthesia has persisted for about a year after immersion in water at 5° to 7 C but not at 10 C. Probably the critical point with reference to nerve injury is the difference between 10 C. and 5 C. Someone mentioned 8 C with reference to blood cells That is a crucial point.

Edholm We have carried out an experiment which I mention only in case others have made similar observations. We measured the forearm blood flow with a plethysmograph filled with brine at an initial temperature of −2 C. There was no great discomfort except in the initial few seconds The temperature rose rapidly in the plethysmograph to 8 C and it was then refilled with cold brine This had to be repeated at intervals so it was not a good experiment as regards temperature control. The total period of exposure to low temperatures that is, between −20 C. and 8 C was rather less than an hour Twenty four hours afterward there was a very marked hyperemia of the whole forearm in the immersed area, and there was some tenderness along the course of one vein which persisted for some three days. The second day there was very definite tenderness along the course of the vein, although no signs of thrombosis could be felt there I mentioned this as possibly an injury phenomenon

which had occurred after a very short, or relatively short, period of exposure to moderate cold.

Minard Mr Chairman, I should like to mention in that connection an observation on a subject following a forty minute immersion in water at 4 5 C. About thirty-six hours following the immersion, a macular eruption appeared over the trunk and persisted for about two days. With no other apparent cause, this eruption seems to have been related to the immersion.

Talbott In sea water?

Minard Yes, this was an immersion in sea water at Argentia Newfoundland

Behnke One of the most remarkable immersions in cold water was related to me recently by Dr Sverdrup Director of the Norsk Polarinstitut, Oslo Norway It occurred during the Norwegian British-Swedish expedition to the Antarctic last year A young Swedish photographer was with two companions in a boat that was carried under by the current. His companions drowned and he was immersed in water at a temperature of −1 5 C. He swam a distance of over 200 meters, wearing Arctic clothing, until he reached an ice floe. The exposure time in water was perhaps a half hour On the ice floe the temperature was −12 with the wind blowing His statement said Got over on a large ice floe. I froze terribly in the −12 C. cold air Kept moving, running around on the floe. I lost *my cap and gloves, but I had my anorak on, and that protected me against* the wind

Burton This is −12 C.?

Behnke Minus 12

Burton That would be Centigrade, wouldn t it?

Behnke Yes He continued The sun appeared and warmed me I could now get off my trousers and boots, empty the water and dry my socks I kept constantly moving to keep the blood circulating The boat finally reached me, and I obtained dry clothing This was 2 00 P.M., after I had spent thirteen long hours on the ice floe I had some warm coffee. I walked to Maudheim, where I immediately turned in and went to sleep. I have had no ill effects from the exposure.

His companions thought, before he went on this Antarctic expedition, that he might be too delicate to be exposed to cold weather He did pretty well

Here is a picture of the ice water in which he was swimming and here is a picture of the survivor He is not athletic. He is a young man of about twenty two years of age and about 6 feet 2 inches in height.

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ACCLIMATIZATION

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WELL, WHAT I am going to say this afternoon will I hope, contain a large amount of speculative material, so that people can discuss the whole subject of acclimatization.

There are a number of people like Adolph, who do not believe that there is such a thing as acclimatization to cold (1) in man, although he does say that there is acclimatization in animals. Furthermore there is the problem of what, precisely you mean by acclimatization. Most people take the word acclimatization to mean, in a teleological sense, a *good* reaction on the part of the body which protects it from the environment. I think, however, we have to realize that there may be reactions of the body to prolonged climatic changes which, in terms of teleological thinking, are not good reactions.

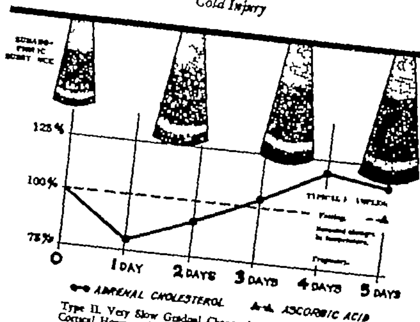
In animals there definitely seems to be an acclimatization to the cold, and Colonel Blair is going to talk later on about the development of resistance to cold. Adolph (2) has recently shown that in rats there is a significant increase in the mean resting oxygen consumption after the acclimatization, and he feels that this is the essence of acclimatization in animals. One would like to know whether this same sort of change is true for adrenalectomized animals, because the whole problem of the adrenal gland in acclimatization, I think, needs some discussion.

I have two slides here to remind you of the effects of cold on the adrenal. This is something I am sure you know about, but we might show them nevertheless.

The first slide (Figure 26) is a composite chart by Sayers and Sayers (3) that shows the type of change you get in the adrenal gland during acclimatization to changes in the environment. This shows, as you can see, some changes in adrenal cholesterol and very few changes in ascorbic acid.

In acute exposure to cold, over one hour at 3 C., this next slide (Figure 27) shows a drop from about 450 to 300 mg. of ascorbic acid in the adrenal gland when cortical hormone is *not* given, but no drop when you protect the animal with cortical hormone prior to exposure. These two slides show a clear relationship between adrenal activity and exposure to cold and are expressions of acclimatization.

In discussing acclimatization to cold in relation to man, the problem of



Type II. Very Slow Gradual Change in Environment.
Cortical Hormone Requirement: Slow Gradual Increase
Pituitary A.C.T. Activity: Slow Gradual Increase

FIGURE 26 Type adrenal response. The actual size of the adrenals is proportional to the total distance the diagrammatic section of the adrenal cortex extends below the upper bar. The data on sudanophilic substance are taken from the observations of Whitehead (*J. Path. & Bact.* 54, 169 (1942)) on fasting animals. The data on size and cholesterol concentration of the gland represent the actual changes found by Ludewig and Chanutin (*Endocrinology* 38, 376 (1946)) to occur in fasted rats. The changes which did occur in the cholesterol content of the adrenal are not considered significant. In the case of adrenal ascorbic acid, no data are available for periods of fasting less than five days. However, fast of six days (*Endocrinology* 32, 103 (1943)) seven days (*Endocrinology* 31, 276 (1942)) or even ten days (*Endocrinology* 24, 673 (1939)) produces no significant change in adrenal ascorbic acid. Reprinted by permission from Sayers, G. and Sayers, M. A., *Ann. New York Acad. Sc.* 50, 522 (1949).

time relationships comes up and we, that is, Robert E. Johnson and I (4) think of its effects on man in terms of three time periods acute exposure to cold, the short-term effects of cold, and the long-term effects of cold.

I will rapidly go over some of the material in the literature, and then we may discuss, later on, perhaps, some of our work that was done in 1947.

The acute reaction to the cold in man is possibly related to the posterior hypothalamic heat control centers. As we know on exposure increased body metabolism develops owing to increased muscle tone and shivering. This muscle tone and shivering, as I said this morning, is related in a linear fashion to oxygen consumption. But the other thing about it is that it can be voluntarily inhibited for a long period of time. In studies made by Glickman (5) with conscientious objectors, they consciously inhibited their muscular shivering and increased tone voluntarily for periods up to

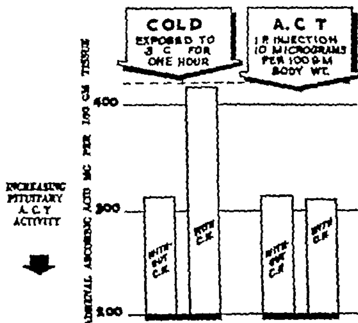


FIGURE 27 Mode of action of cortical hormone in preventing reduction of adrenal ascorbic acid upon exposure of the rat to stress The level of the dashed line represents the concentration of ascorbic acid in the adrenals of untreated rats The heights of the columns represent the concentration of ascorbic acid in the adrenals of treated rats The distance the top of column extends below the dashed line is proportional to the amount of A C T H elaborated by the pituitary or to the amount of this trophic hormone injected intraperitoneally Reprinted by permission from Sayers, G and Sayers M A *Ann New York Acad Sc* 50, 522 (1949)

a half-hour at which time the deep body temperature was falling, so that one wonders whether anything but a simple reflex is involved in that type of body reaction to cold. It does not seem to be mediated by hormonal excretion, nevertheless we need data, not only of epinephrine content of the blood but also of the nor-epinephrine content of the blood during acute exposure to cold.

Now when we come to short term effects of cold — but let me go back a second. We know that all investigations have found a redistribution of water from the blood in acute exposure to cold. There is a hemoconcentration and a diuresis and one wonders how that is initiated is it a reflex phenomenon or is it initiated through an endocrine gland? There is no evidence in the literature whatsoever to show whether it is initiated by the one or other but I suspect it is reflex in origin

When we come to the short-term effects of the cold on man, I find the following in the literature which suggests acclimatization First of all,

Freeman, Pincus, and Glover (6) have shown that urinary 17 ketosteroid excretion is increased in man on short term exposure to the cold. Keaton and Mitchell (7) have shown that the tolerance to the cold is increased by a high carbohydrate diet, and there is also suggestive evidence that between-meal feedings or multiple feedings, influence favorably the tolerance to cold.

Stem and Bader (8) demonstrated equivocal evidence of pituitary adrenal stimulation in the cold.

Bass (9) recently has shown that there are no specific changes in the eosinophils or uric acid/creatinine ratio in men exposed to the cold. I don t know anything about that investigation. I saw the abstract in the *Federation Proceedings* Perhaps Colonel Blair will tell us some more about that.

Daniels (10) working in the same laboratory as Bass, the Climatic Research Laboratory writes that there are small co-ordinated changes in many responses rather than a striking change in any one function, with indications of reduced physiological strain being evident. Is that correct?

Blair Yes, that is correct, I heard Dr Bass s and Dr. Daniel s presentations at the Federation Meetings in Cleveland, and discussed with them the reason why they failed to get any increase in eosinophil count. My own impression was that the cold stress under which the men were placed may not have been severe enough to elicit an eosinophil response. Twelve subjects dressed in shorts, were exposed about twenty hours daily for twelve days to a rather moderate degree of cold stress, namely 60 F Greater cold stress may be required to bring about an increase in eosinophils

Kark In trying to determine whether there was a true increase of metabolism in men exposed to cold, Horvath and his colleagues, and Gray and Consolazio and I (11) did studies of oxygen consumption on men wearing Arctic, temperate, and tropical uniforms in different temperatures, and in those studies we found that there was only a 2 per cent increase in heat production in the cold as compared with the other climates, over and above the type of clothing that the men were wearing at maximum work rates So there does not seem to be any really true or tremendous increase in specific heat production in man as there is supposed to be in animals exposed to cold But we did not do these studies on acclimatized men The subjects were unacclimatized.

Horvath Our studies were on unacclimatized men, if you assume that being in the environment fourteen days is not acclimatization. I myself don t think that fourteen days of exposure to a cold environment means anything in terms of acclimatization. At least they were being acclimated. They may have started being acclimatized

Kark We also showed on the Musk Ox expedition (12) that there is

a diminished excretion of ascorbic acid in soldiers in the cold, but when we studied soldiers in Shilo (13) there was no diminished excretion. In fact, there was an increased excretion of ascorbic acid. We also found that there was an increase in excretion of urinary creatine in short-term exposure to the cold.

When we come to the long-term effects of cold in man, I am one of those who believe that there is acclimatization. The clinical data that you find are as follows: increased hunger and the laying down of "fat." I put "fat" in quotes because I don't know what it is that increases the body weight of subjects. But if you take groups of soldiers in the tropics and groups of soldiers in the Arctic and get their average weight, as we have, we find an 8 kg. difference. And anybody who has been up there knows how hungry you get and how hungry everybody else around you gets, and how everybody eats and puts on "fat."

Talbott: Don't you get hungry as soon as you get up there? You don't have to wait for two weeks before you get hungry. You start right in.

Kark: You start right in, and then you eat tremendously until you reach your maximum weight for the climate. Thereafter you eat at a higher rate than you do in the tropics or in temperate climates.

This slide (Figure 28) shows voluntary caloric intake in soldiers in

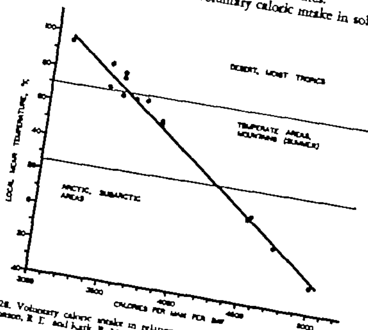


FIGURE 28. Voluntary caloric intake in relation to temperature. Reprinted by permission from Johnson, R. E. and Kark, R. M. *Science* 05 378 (1947)

in doing histology in the North, there was some trouble about fixation, and for that reason they had these livers that looked like fatty livers but without stainable fat in them. It was the following year that they showed glycogen.

Edholm Weren t there fairly rapid changes in the size of the enlarged livers during the period they were up there?

Burton I don t remember the changes in size. He did try some dietary experiments, and in some cases was able to change this back to what one would consider normal in other races — by changing the diet. But I don t remember the details

Sellers Well, first, as I said, from a clinical point of view they felt that they were dealing with fatty liver so they decided that treatment with lipotropic factors would be a reasonable course to follow but they did not have any successful results with them. I think with mixed vitamins, large amounts of B complex, or with milk powder there was a decrease in the size of the liver in a matter of a few weeks.

Burton I think in your general review of definite evidence of acclimatization to cold, I should also like to include the work done by Mackworth several years ago He is, I think, one of the few persons who has definitely produced evidence of acclimatization. He took a group of men at Churchill, some of whom were living outside and were really exposed to cold, and others of whom were living as most do in Churchill in overheated barracks, and did a test of tactile discrimination Very definitely there was a statistically val d difference between the two groups. There was also a difference in the behavior of their skin temperatures. So I regard that as one of the very first objective pieces of evidence of acclimatization to cold

Edholm May I speak of that, Mr Chairman? I have the paper here. Dr Mackworth very kindly gave me a preliminary draft before I left. The gist of it Dr Burton has already given you.

Dr Mackworth has continued this work in England exposing his subjects in a cold chamber again wearing ordinary clothing, at a temperature of approximately -10 C. For a period, initially of one hour daily they sat in this chamber At the end of the hour one finger was exposed over a local wind tunnel, the air speed being of the order of 500 to 600 feet per minute. The finger was held in this air current for two minutes. The tactile sensitivity was measured by the two-point tactile discrimination technique before and after exposure, so it was possible to study the degree of finger numbness and to measure the rate of recovery

In the subjects who were exposed for an hour daily there was no very obvious trend in the changes in the degree or duration of numbness following this exposure. Mackworth then tried an exposure of two hours daily and when he did that, during the first two weeks there was a marked

decrease, a steady decline, in the loss of tactile discrimination following the exposure, and in the recovery time. Thereafter for a further four weeks, the change was minimal. Acclimatization developed during the first two weeks, and then did not proceed further

There was one rather curious observation, which may or may not be substantiated by further work. It so happened that there was a period of hot weather during this experiment, lasting only a few days, and the acclimatization, if I may use that word, disappeared during that hot weather and then had to be re-established. I don t know the time relationships of the re-establishment of the subsequent acclimatization after the hot weather but I think I am right in saying that it was a good deal quicker than the initial one.

Kark Another interesting phenomenon is that basal metabolism rate changes only slightly in man from the Arctic to the tropics, a difference of not more than 15 to 20 per cent (14)

Then there are two other observations of acclimatization, the first made by Glickman (5) in which he used subjects acclimatized to long exposure at −20 C. with considerable protective clothing He took these people next into a room at 60 C., either naked or wearing very light clothing, and found that with standard exposure there was a much smaller drop in rectal temperature than there had been before the period of acclimatization Now that may mean that the subjects had learned to shiver efficiently

The second piece of evidence is the report by Schmidt Nielson of low melting point fats being found in the periphery of man as compared with the warmer parts of the body The surface fats of cold-exposed pigs have a much lower melting point than the surface fats of pigs in the warm or of pigs protected from cold by being wrapped in sheepskins.

Now I want to go on to our study at Camp Shilo in Manitoba, Canada, in the winter of 1947 but before I do that I think we ought to speculate a bit about ACTH and I want to say a few things here about the pituitary-adrenal axis. I might think differently about it two years from now or next year The reason for this diversion is that when we did the study in 1946 or 1947 I was convinced that we had a pituitary adrenal response to cold, but as we get to know more about the clinical use of ACTH, I am not so certain.

First of all I think we all know that the effects of exogenous animal ACTH are not the same as endogenous ACTH, that there is probably more than one ACTH in man and that these may stimulate different parts of the adrenal gland (17) Then we have all learned that there is a wide variation in response to ACTH by different individuals besides each individual having his own "biochemical fingerprint" of excretion of the different steroids (18) The response of any particular organ to ACTH

depends upon its status or priming at the particular moment that the ACTH is given For example, in well fed people, if you give ACTH you get ketonuria. If you have a starved person who develops ketonuria and you then give him ACTH, the ketonuria disappears. What I am trying to get at is this if you take a group of people up to the Arctic and study their adrenal response to the cold by various measurements, you might find a wide variety of reactions, but I don t think you are going to find a very uniform type of reaction. We certainly had wide variations in data from the Shilo study

As far as eosinophils are concerned as far as the urea-creatine ratio is concerned, and as far as other means of measuring adrenocortical activity are concerned, our group has become very skeptical of a number of these measurements (19)

I want to show you two things about eosinophils, since everybody seems to use the eosinophil count as an index of adrenal activity This concept is incorrect, I feel sure.

These slides (Figure 29 and 30) are from some of my colleagues who

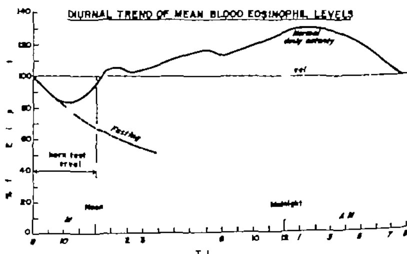


FIGURE 29 Diurnal trend of mean blood eosinophil levels. Modified from Rud. All normal subjects 23 from 8 A.M. to 6 .M., 6 from 6 .M. to 8 A.M. and 12 partial or complete fasting from 8 .M. to 6 .M. Reprinted by permission from Best, R. W and Samter, M.: *Blood* 6, 61 (1950)

are working with me on eosinophils. These are just to show the diurnal trend of mean blood eosinophil levels in man when he is fasting and when he is eating normally (20) You see, there can be considerable drops during the four hour period during which most of us do Thorn tests.

Figure 30 shows representative absolute eosinophil counts in an individual as well as the wide fluctuations that can occur from time to time.

Moreover recently Biermann (21) of California has shown that simple things like doing a Valsalva maneuver can produce a marked eosinopenia. Changes in respiration certainly can alter the eosinophil count. So I think we have to be very chary about using the eosinophil as a measure of adrenocortical function.

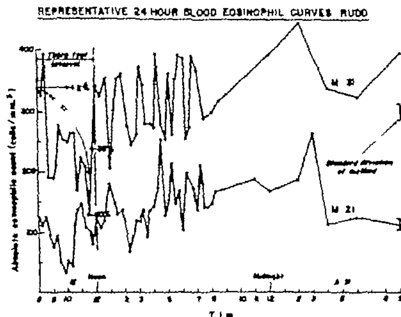
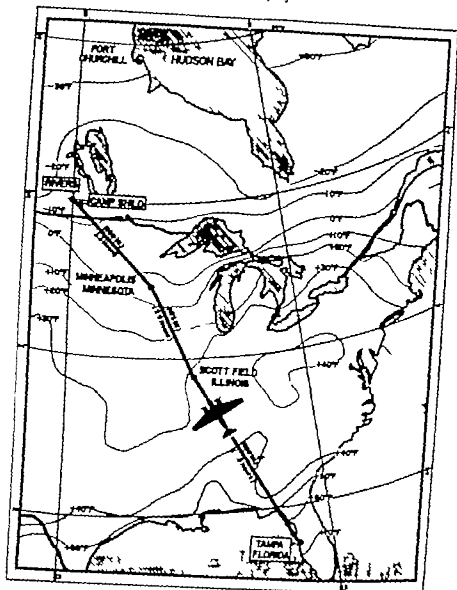


FIGURE 30. Two representative twenty-four hour blood eosinophil curves with emphasis on possible errors of comparing 8 A.M. and noon eosinophil levels. Data from Rudd. Short time fluctuations may be compared with [illegible] at different levels. Reprinted by permission from Best, R. W. and Samter, M. *Blood* 6: 61 (1950).

Ephraim Short has also shown that the uric acid-creatinine ratio can be much altered by differences in diet (22) so we cannot use that as an index of adrenal function.

Now in our study (Figure 31) which was made in the winter of 1947 (13) we used as subjects thirty-two young volunteer soldiers in Florida who were acclimatized to heat. We put them into aircraft and flew them up to Camp Shilo near Winnipeg in midwinter and from the aircraft they were put into the field for a period of eleven days. The temperature went down to −45° but fluctuated up and down. Then they were moved out of the field and studied in warm barracks for three days. All



The air route of the test troops is shown from Tampa, Florida, to Rivers Air Base, Manitoba, Canada, with fuel-stops at Scott Field, Illinois, and Minneapolis, Minnesota, 20–21 January 1948. Latitude and longitude are shown along the map grid. The isotherms, derived from U. S. Weather Bureau data, are representative of the time of day at which the flight passed the given points.

FIGURE 31 Travel itinerary of test troops. Reprinted by permission from Bly, C. G. et al. *Armed Forces Med. J.* 1, 615 (1950)

sorts of measurements were made, which I don t propose to discuss today but there are certain data which might be of interest.

First of all, two evidences of changes in hormone activity in the subjects were noted. In them, their normal protein-bound iodine, of 6 4 gammas per 100 ml., dropped down to 3 on the eighth day and to 3.0 on the eleventh day No protein-bound iodine measurements were made there after unfortunately

Gottschalk This occurred in all of the subjects?

Kark All subjects in which the measurements were made.

Gottschalk How many subjects were there?

Kark I think they were made in ten subjects altogether ten or twelve. In every one of them there was a very uniform drop

Second, in the well fed group there was an increase excretion of urinary 17-ketosteroids from 16 to 20 mg. per day but in the subjects who were on low-calorie diets of about 1 000 calories to 1 900 calories a day there was no increase in 17-ketosteroid excretion

The other interesting phenomenon is the finding of ketonuria in well fed inactive men in the cold We have studied ketonuria in the cold (23 24) You see three types. You see a starvation ketonuria, you see the postexercise ketonuria of Curtis and Douglas, and then you see this peculiar cold ketonuria. And I m just suggesting that the cold ketonuria is the same type of ketonuria that you see in some people when you give them either ACTH or cortisone

We also did in these people (F gure 32) a Robinson-Power Kepler diuresis test (25) in which we restricted water in the beginning, measured maximum concentration in the morning, gave them 20 cc per pound body weight to drink, and then measured not only the rate of excretion, but also the minimum specific gravity This test is one which is used for the diagnosis of Addison s disease In Addison s disease you get a delayed diuresis after water loading so that you find that the overnight specimen of water is of a greater volume than the greatest excretion of water during any single period in the morning, with a ratio of below 1

What is it, about 0 5 is it, in Addison s disease?

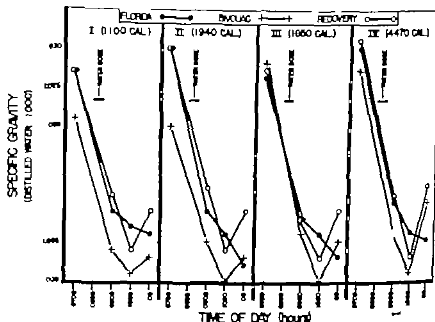
Conn No he sets up a formula which includes urine volumes as well as concentrations of blood and urinary sodium, chloride and urea. So far as the initial procedure, the water test itself is concerned, if any single hourly specimen exceeds in volume the overnight specimen, adrenal insufficiency is regarded as having been ruled out.

Gottschalk It is a Kepler Power water test?

Conn Yes, Kepler Power and Robinson

Kark This test showed changes in our subjects which we believe are related to the adrenal function. In one group of men, in a typical experiment, there were changes in ratio of the volume of the largest one-hour specimen over the night volume of 1 88 during the period in Flord-

WATER RESTRICTION — DIURESIS TEST



SPECIFIC GRAVITY OF URINE DURING WATER RESTRICTION—DIURESIS TEST

Ordinates Specific gravity of urine compared with distilled water at the same temperature.

Abscissae For each of the four experimental groups, the time of day during the test. The time needed (0800–0830) to drink the water is denoted by solid bar in the chart. The dose of water was 20 ml. per kilo body weight.

Figure 32. Specific gravity of urine during water restriction-diuresis test. Reprinted by permission from *Survival in the Cold* S G O Medical Nutrition Laboratory Report No. 42, Nov 30, 1948 (Fig 28)

2.22 on the eleventh day of being in the bivouac, and then during recovery it went back to 1.23

And here again you see in this slide that there are changes away from the Florida level during the bivouac in all groups, and then a return, due to recovery toward the Florida type of curve but not exactly the same.

Mowrey By that, Dr Kark, you mean that the largest hourly day specimen was two points higher than that of the night?

Kark No when you compare the volume of the one-hour specimen over the night volume —

Mowrey The ratio between those two

Kark Yes, the ratio between the two

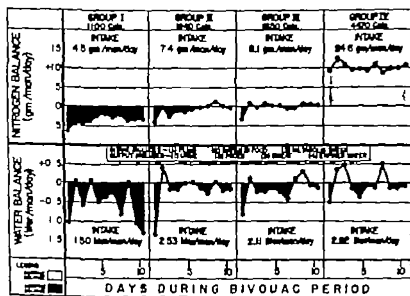
Conn Do you know whether that can be related to the skin losses of water in Florida as compared with the skin losses in the North?

Kark It may be I doubt it.

Birch What about these changes of filtration just presented by Dr Talbott?

Kark It may be related to that, but certainly it is a true phenomenon. As far as the nitrogen balance is concerned (Figure 33) let s disregard

NUTRIENT BALANCE — NITROGEN WATER



Ordinates Top Nitrogen Balance grams per man per day
Bottom Water balance, liters per man per day

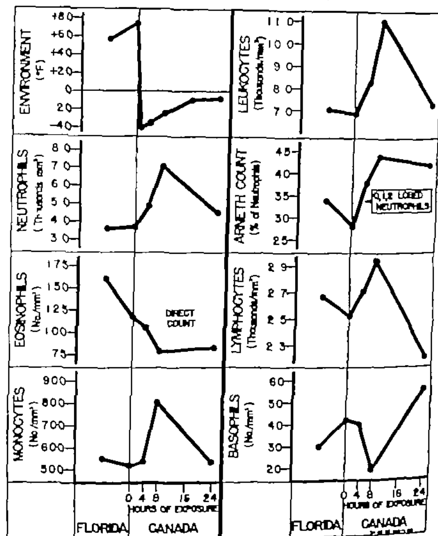
Abscissae Groups and day in bivouac period Intakes for each group are shown in appropriate boxes.

FIGURE 33 Nutrient balances—nitrogen and water Reprinted by permission from *Survival in the Cold* S G O Medical Nutrition Laboratory Report No 42, Nov 30, 1948 (Fig 28)

the low calorie groups. Note that in Group 4, taking as much food as they want, there is absolutely no evidence of a catabolic phenomenon.

As far as the water balance is concerned, we now come again to the first day of acute exposure, in which we found maximum diuresis within the first eight hours (Figure 21 p 123) I want to show the water balance there. You will see that there is a negative water balance, that is, a diuresis on the first day in all groups. In the 1 100-calorie group you will see a marked water diuresis practically throughout the whole period of study We believe this is involuntary dehydration due to ketonuria, which we have noticed before.

Figure 34 shows some acute effects of cold on hematology Here



Ordinates Environmental temperature (°F); leukocytes (thousands per mm³); neutrophils (thousands per mm³); Arneth count (plotting only the percentage of neutrophils with one and two-lobed nuclei); eosinophils (number per mm³); lymphocytes (thousands per mm³); monocytes (number per mm³); and basophils (number per mm³)

Abscissa Florida average; hours of exposure to cold in Canada

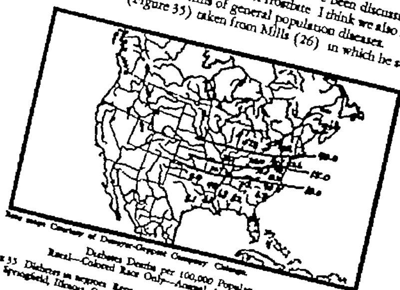
FIGURE 34 *Acute exposure to cold—hematology. Reproduced by permission from Survival in the Cold.* S G.O Medical Nutrition Laboratory Report No. 42, Nov 30, 1948 (Fig. 33)

you see the neutrophils rising, the leukocytes rising, an increase in the Arneth count, the eosinophils dropping. The eosinophils stayed down throughout the whole period of study in the field, and then went up again. I don't know exactly what that means, but it is possibly adrenal overactivity. The other changes returned to normal very rapidly.

Now I just want to make one speculative statement, and then I will stop.

What I want to say is this: nearly all of us have been discussing cold injury in terms of local injury in terms of frostbite. I think we also have to think about cold injury in terms of general population diseases.

This is a slide (Figure 35) taken from Mills (26) in which he studies



Diabetes Deaths per 100,000 Population
Rural—Colored Race Only—Annual Average (1931 35)

FIGURE 35 Diabetes in negroes. Reprinted by permission from Mills, C A *Medical Climatology*, Springfield, Illinois, C C Thomas, 1939

the rate of diabetes in Negroes who have moved from the southern United States to the North, and in which he shows that in the colder areas there is a higher incidence of diabetes than in the warmer climates. Whether this is related to any endocrine imbalance or whether it is related to the fact that in colder climates people eat more, and that when you eat more you get diabetes, I do not know. But there are other diseases which seem to occur at higher rates in a northern climate, and it seems to me that the long-term effect of stress of cold on man is something that needs study. Very often I wonder what the climate of my own town, Chicago, does to a human being's health. It has a tremendous diurnal variation in temperature.

Burch Was that chart on the Negro taken from Vital Statistics records, or is it from hospital records?

Kark Those are various types of records that Mills took from Vital Statistics and from hospital records

Burch Because the differences in diagnostic facilities may account for a part of the differences shown.

Kark I think so

Burch The hospital facilities in the South are not as good.

Kark His ideas have been very severely criticized by Harrington, as everybody knows, but I just put it forward as a speculation I have a feeling and I may be wrong, that our group here should not confine itself purely to thinking over the next five years, in terms of frostbite and hypothermia.

Burton I should like to raise one very important point, which I learned secondhand, as to any pituitary-adrenal response to the stress of cold. This was the result of a conversation with Jean Manery Fisher who with Dr. Ken Fisher is up at our Northern Research Laboratories at Churchill, and has been working there for the last two years. They have been setting up tests to measure in every way they can the adrenocortical response. She said that they were convinced that you could demonstrate a response quite easily on the soldiers who are posted at Churchill when they go out for a couple of weeks on a sort of indoctrination to the cold course. But the thing that worried her was whether this response was related to the cold or to psychological factors, because it is so difficult to separate them. The men all are a bit worried about going out at 30 below in the wind and living in tents They are keyed up and the results of other people would show that that amount of anxiety and so on, could produce quite as great a response It must be a very difficult thing, in all such experiments, to separate these factors, because it is a psychic trauma, in a way to be sent out on one of these schemes

I am wondering, Dr Kark, whether that could be excluded in the experiments you spoke of

Kark We did Minnesota Multiphasic Personality Inventory on all of our subjects, and we did very detailed psychological studies. There were changes in their psyches during the period of time they were in the cold, and I am sure —

Burton How are we ever to rule out anxiety? It is very difficult, isn t it?

Kark I can think of one thing that might be worth doing — and I think this ought to be a combined Army Air Force, and Navy project — and that is to study the adrenal glands in men dying a violent death in the North, in Arctic areas, against those in men who die a violent death in the temperate climates or tropic climates. It seems to me that that is the kind of project that could be set up by the Army Institute of Pathology We tried to start one like that some time back, but failed. With today s greater interest in cold, perhaps we could get such a study going

Talbott Do you think, Dr Conn, that you could get information from the histological picture of the adrenals that would help answer this problem?

Conn I don't know what the long term histological picture might be. It is much more likely that histologic effects in the adrenal gland from stress will be more evident in the early period of the alarm. I am of the opinion that final adaptation to a stressing circumstance involves a series of mechanisms which are not the same for each type of stress. The *initial* response of the pituitary-adrenal mechanism to stress is probably uniform for all forms of stress, that is a complete mobilization of all possible bodily defenses. What goes on after that is likely to depend upon the type of chronic stress to which the organism is being exposed upon the form of injury which needs to be combated specifically.

I should like to comment on Dr Kark's P B I findings. Apparently the most constant thing that Dr Kark noticed was reduction in P B I in the blood of his subjects. Some of you know that reduction in protein-bound iodine is characteristic of long-continued administration of ACTH or cortisone to normal individuals. Apparently either cortisone or ACTH is capable of decreasing pituitary thyrotrophic hormone activity and thereby reducing thyroid function. Despite this reduction in thyroid function, in people given long-continued ACTH or cortisone oxygen consumption is maintained at or near the prior level. This means that the peripheral activities of cortisone or cortisone like materials include a calorogenic activity which is independent of thyroxin activity. On the other hand, if one gives ACTH to a person whose P B I is low to begin with, a myxedematous patient, the adrenal response is deficient. If protein-bound iodine in these experiments really represents a decrease in thyroid function, then it could be that because the adrenal gland cannot respond normally we are faced with a complication which would tend to diminish pituitary responses as we usually measure them.

Kark Yes, I see what you mean.

Mowrey What do you mean by prolonged action? In weeks or months?

Conn Three or four weeks of continuous ACTH or longer.

Gottschalk I should like to tell you about some studies we made of serum protein-bound iodine and basal metabolism in a group of seven soldiers that were studied first at Fort Knox, Kentucky and then in the Canadian Arctic. During this time many other studies were done on these men. I might add that I am sure we can put a great deal of trust in these values for protein-bound iodine as they were done by Dr Douglas Riggs in the Department of Pharmacology at Harvard Medical School, for he has a very good method for determining protein-bound iodine.

These seven men were studied at Fort Knox until the first of January when they were transferred to Fort Churchill, Manitoba. There they lived

in heated barracks and were outside in the cold for three to five hours daily On the first of April they were brought back to Fort Knox and observed there for another six weeks. Throughout this time we could detect *no significant change* in the basal metabolism and protein-bound iodine of any of the subjects. There was a slight decrease in the average protein-bound iodine while the subjects were at Churchill, although there was not a significant difference in the Churchill versus the Fort Knox values.

Kark Do you remember what they were?

Gottschalk It was a matter of approximately one half a microgram per cent. It was a very small change.

It is also interesting to note that one of these men had serum protein-bound iodine values in the myxedematous range, and yet we could detect no difference in his tolerance to cold He certainly suffered no more than the other men at Churchill

One summer we had the opportunity to draw blood from a group of seventeen Eskimos, ten of whom were from Southampton Island, Northwest Territories and seven from Chesterfield Inlet, N W T Their protein-bound iodine averaged higher than that of a large group of euthyroid patients at the Massachusetts General Hospital. Most of the Eskimo values fell within our normal range, although there were some in the hyperthyroid range.

Careful physical examinations were done on all of these Eskimos, and there was no clinical sign of hyperthyroidism I might also mention that in none of these seventeen Eskimos were the livers palpable.

We do not know the cause of the high protein-bound iodine values in the Eskimo group It is apparently not a matter of temperature, since the blood samples were taken in the summer when the temperature was about 45 F It is not a matter of insufficient washing of the blood samples so that total iodine rather than protein-bound iodine was determined, for all samples were washed sufficiently to remove any amount of nonprotein iodine. It was thought possible that perhaps the increased iodine in the diet from sea food — these are coastal Eskimos, and they eat much fish — was sufficient to raise the protein-bound iodine, for it is possible to raise the serum protein-bound iodine by ingesting very large amounts of inorganic iodine But if you calculate the amount of iodine that these Eskimos could possibly have ingested from a pure fish diet, it falls far short of the amount needed to raise the protein-bound iodine.

Kark These Eskimos were studied during the summertime?

Gottschalk Yes, during the summertime.

Kark Well, I don t see why Eskimos cannot acclimatize to summer temperatures, just as we do Certainly on the Musk Ox expedition, when the men moved from a temperature, I think, somewhere around —45 C toward a temperature of 0° C. — in other words, from a very cold to a

freezing temperature — there was very definite evidence of acclimatization to heat of the same order of heat acclimatization that Joe Doupe and Barett (27) found in men in midwinter who went into a warm room.

Burton I don t know the protein-bound iodine values for a group of Englishmen I should think that if you wanted to work on acclimatization in man, you should study a thousand Englishmen sitting in their offices, particularly civil servants, at a temperature of 55 or 60

Has anybody got comparable figures — hospital figures — protein-bound iodine figures from England and from the States? Do you know Dr Edholm?

Kirk Myant at the University College Hospital London?

Edholm I am sure there are some figures, but I do not know anything about them.

Siple I should like to second your suggestion concerning the British. I believe they are probably the nearest to the cold-acclimatized people in the sense that as we go into Canada and the northern portion of the United States and into other cold areas, both with clothing and houses we tend to give ourselves a tropical environment. Under the limitations of England, we have reached just about the bottom threshold, which is evidenced to some extent by the amount of chilblains and snuffles which show up among the British as a whole.

Burton I know I would have more cold stress spending a winter in England than I would spending two weeks bivouacking at Churchill

Kirk Of course, I want to point out this about our men they were under cold stress for a period of eleven days and nights they were never in the warm. They were cold all the time, even in their sleeping bags When they got out of a warm aircraft and the warm barracks, they were taken straight out into trucks, the temperature 45 below zero Fahrenheit, and driven about fifteen miles, with a blast coming in at the back of the truck, until they got into the field. They were really exposed to cold as compared with most people who go to the North and live in tropical environments.

Birch Coming back to Dr Burton s statement when I was in England two or three years ago I made an observation that impressed me very much, a purely clinical observation, concerning the appearance of the hands of the people in England, Wales, and Scotland Dr Edholm s hands show the changes very nicely I have noticed his hands since he has been here. His hands are quite different from ours They are extremely inflamed. In studies such as he has been describing, one often wonders about the influence of the vascular state. Such alterations in the vessels of the skin of the hands seem to be characteristic of most of the people of England.

Burton Did you ever see chilblains on this Continent?

Burch No

Burton Yet everybody has seen them in England.

Burch When visiting Scotland, I found the changes to be even greater The face and ears are also considerably involved.

Kirk Never mind England and Scotland You see them in Capetown in the winter where it never freezes but where temperatures go down to +40 or +50 F There is a high incidence of chilblains among the population there, especially young females There is no central heating, but open grate fires are found in the houses

Burch Are the hands injured or acclimatized?

Edholm Of course, we have not really got down to a definition of what injury means I am waiting for the pathologists to tell me what the difference is between a pathological process and a physiological process in the problem of the effect of cold

Blair I shall ask Dr Burton and Dr Edholm a question. Among the numerous cases of chilblains in England have you ever seen it develop in a Canadian or American while residing in England? During two winters in England I saw many cases of chilblains, but I cannot recall a single case among the many Americans and Canadians there at the same time.

Mowrey Among American WACS over in England, it was almost universal in the wintertime

Blair Just among the WACS and not among the male soldiers?

Mowrey The males did not get chilblains but the females did, because of the exposure that they received.

Blair The Americans and Canadians to whom I referred were all male college students I have never observed chilblains in a Canadian or American on this Continent or in England

Mowrey You will see it among females at college in the wintertime.

Gottschalk Would someone care to define chilblains ?

Edholm I don t know that I can give you a very clear description, Dr Gottschalk. There is swelling and hyperemia of the digits as a result of exposure to moderate cold, which may in a severe case go on to actual sloughing of the skin The swelling and hyperemia may persist for many days Chilblains do not commonly progress to the state of ulceration, but that may happen (28 29)

There is a higher incidence in adolescents, and it appears to be commoner in women than in men. That may or may not be due to differences in clothing

Gottschalk Just hands?

Edholm Chilblains occur on hands and feet, and may occur round the ankle. You can also occasionally observe chilblains of the ears.

Blair Is there not also fairly strong statistical evidence to support a hereditary factor in chilblains? At least the incidence appears to be much greater in certain families than in others.

Edholm I don t know about that Colonel Blair I have never heard of a hereditary factor in chilblains, but that may be just my ignorance

Siple It is unfair to assume that it is the mildest form of trench foot — in other words, just a bare touch of it rather than the severe case that we generally think of in trench foot

Morrey I think the answer to that is covered n T F Whayne s (30) thesis on cold injury in which he classifies chilblains — acrocyanosis — as being the mild type of cold injury If I recall correctly he gives the incidence in females as about three to one over males, and says that the location of it in females is primarily over the anterior surface of the tibia.

Sellers Mr Chairman, as an addition to the discussion on the effects of cold on the thyroid, the hyperplasia that occurs in the thyroid, such as Ring described, occurs rather gradually and the hyperplasia can be pre vented in part by giving sodium odide in the drinking water although it is only a partial prevention (31)

We have also obtained evidence that there is an increased amount of thyrotrophic substance in the pituitary after exposure to cold. We did not estimate TSH in the blood because we did not know how to do so

There are some further emarks on acclimatization in animals that I should like to make either before or after Colonel Bla r

Kark I wonder whether we could give Dr Conn a chance to say any thing more that he wishes because he has to leave early this afternoon, and there may be some things he wishes to say

Conn No Did you have any particular thing in mind

Kark No

Conn I think that I might throw into the discussion for wherever they might fit, one or two additional points

The phenomenon of so-called corticogenic hypothyroidism from long continued administration of ACTH or cortisone is probably an artefact and not applicable to spontaneous activation of the pituitary gland. If one gives epinephrine he can show not only evidence of a release of ACTH from the pituitary but also of thyrotropin and perhaps other things as well. It is very likely that during spontaneous alarm from stress, many things besides the release of ACTH occur which may modify significantly what we know to occur when we give an injection of ACTH to a normal person that is to say the spontaneous metabolic effects of stress may not be precisely what we think they should be as we have learned them from an injection of ACTH into a normal person

Further the utilization of steroids under conditions of stress may be entirely different from the utilization of steroids artifically produced, in the absence of stress by the administration of ACTH I think ll of these factors might be important in considering what would appear on the sur face to be absence of metabolic evidence of stress as we ha e learned it from ACTH

Kark Do you want to say anything about Selye's work?

Conn With respect to diseases of adaptation?

Kark Adaptation in relation to the cold, specifically the fact that he produced nephritis by cold injury to rats.

Conn I think most of Selye's ideas are pretty well set forth by himself in the Transactions of the Josiah Macy Jr Foundation Conferences on Adrenal Cortex and elsewhere.* I think that you can pick those up much more easily from him than from me. He has them all outlined well and clearly

Talbott Dr Conn, the increase in fat that Dr Kark observed, at least would be in keeping with increased adrenocortical activity would it not?

Conn The increase in fat?

Talbott Fat deposition.

Kark I did not say there was an increased fat deposition.

Conn No he said increased weight.

Kark I said there was increased weight. I do not know if it is fat And, of course, there was increased hunger

Talbott Isn't there some evidence that there is increased fat deposition?

Kark There is no clear evidence, so far as I know that there is increased fat in man in the cold I suspect it is fat

Siple We have not seen any great tendency for man to take on much more fat.

I think the assimilation of fat in their diet, voluntarily is very striking There were individuals who had not been able to eat a piece of fat but who would drink rendered fat from bacon with gusto when they were cold and would revert to not being able to eat fatty bacon when they got back to a warm climate even for just a few days That would happen so sharply that one could observe that even in a one or two-day exposure they could take the fat, and then could not take it when they got back to a warm climate. I don't know what is involved, but I saw it happen more than once.

Talbott You have not done any body density studies before and after acclimatization, have you, Dr Behnke?

Behnke No but if there is a gain in weight, I think it is most likely to be fat.

Kark I think so

Behnke It is not muscle and bone after we have grown up

Kark I think it is fat.

Behnke We should like to think it is muscle and bone, Dr Kark.

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* Selye H *The Physiology and Pathology of Exposure to Stress* Montreal, ACTH, Inc., 1950.

Kark I don t.

Behnke I was not in on the early part of the discussion, unfortunately for me, but has the matter of the relation of anoxia to cold been discussed?

Talbott No.

Behnke About two years ago I attended a high-altitude conference in Peru, and one of the things that came out of this conference was the striking difference between the effects of acute anoxia as contrasted with the lack of findings in individuals who were adapted to high altitude. I mean with reference to glandular changes and disturbance of hormonal secretion. For instance, acute anoxia brought out the hypertrophy of the adrenals, glycosuria, and changes in the thyroid — alterations that were not at all evident in individuals who were adapted to life at high altitude

Now I wonder whether or not in exposure to cold there are changes which take place in various glands which regress after individuals become adapted.

Conn Well, yes, that is what I had in mind when I mentioned earlier the initial versus the final reaction of man to chronic stress. It showed up reasonably well in metabolic studies that we did during the last war on heat adaptation, where, for example the initial exposure to heat brought about negative nitrogen balance independent of the level of intake of protein. During a period of fourteen to twenty one days, as adaptation approached completion, the negative nitrogen balance disappeared The individual was then in nitrogen balance and fully acclimatized Yet there was other evidence that increased electrolyte regulating activities of the adrenal were maintained, as if initially the response to the stress was a complete one, involving all of the peripheral activities associated with increased adrenal function. Then as time went on, depending upon the particular type of stress that had to be combated certain readjustments took place. For example, the negative nitrogen balance was not helpful not required in this particular type of stress, but it nevertheless was brought out during initial exposure, and then it disappeared. On the other hand, salt losses from the skin represented the immediate threat to life, and evidence of continued adrenal activity with respect to salt conservation remained constantly present for months

Kark You think, then, that there is a difference between the types of hormone that are being excreted that initially you get both an m.c. and g c. excretion, and then later just continue with an m c. excretion?

Conn No I don t I think that the response to adrenal hormone is conditioned in the periphery

Sellers Dr Conn, we have found that if acclimatized rats — by that I mean rats that are accustomed to living in a cold room for more than five or six weeks — are adrenalectomized or thyroidectomized, they survive much longer than adrenalectomized or thyroidectomized controls, al

though eventually they do die, indicating that some of the secretion is necessary The difference is very striking indeed (32)

Some of these experiments had been suggested by the work of Selye (33) and also by that of Leblond (34) though not in quite the same connection.

I think it demonstrates the point that you have been making, does it not?

Conn Yes there appears to be some change in the peripheral tissues in addition to the influence that the adrenal has during the course of adaptation.

Horvath How about accessory adrenal tissue?

Kark Which is present in the testes mainly

Horvath Yes There may be other places where it might also be giving the same response and now is working at a slightly higher level

Conn That could be.

Kark I should like to go back to Captain Behnke s statement about there being no glandular changes in long term anoxia at altitude. I recall that Dr Monge (35) told me that there were testicular changes in animals in Peru with sterility and that when he was in Denver he went mountain climbing and talked to farmers at high altitude, and found that their cattle were sterile We know that in long-term acclimatization to anoxia there are definitely changes in the function of at least one gland.

Conn I think it might be pointed out that the histologic appearance of a gland may not give an indication of its functional activity

Horvath Of course, those animals were functionally proved to be of no value if they were sterile It does not matter what their testes substructure looked like

Conn Yes.

Horvath I mean, functionally they were sterile.

Behnke To get back to this other question I think that it may be true in lower animals, but not in man — I don t know whether or not anybody has applied a Kinsey index I don t think there is any evidence of general sterility among the Indians who live and work at 14 000 feet.

Kark Monge wrote a book on *The Deterioration of Civilization in the Andes* in which he described most of the deterioration as being due to the fact that sterility has developed among the population at altitude because of anoxia Wasn t that his philosophy? Do you remember it, Dr Talbott?

Talbott It was a common belief without any statistical evidence, when we were there in 1935 that the Indians at 14 000 feet, both in Peru and in Chile, were less fertile than the Indians at sea level. Did Monge quote any figures in his book?

Kark He wrote the whole history of Peru around that.

Talbott Yes, but did he have values?

Kark I don t remember

Talbott I know it was a general impression. When we were there, he was just beginning to get on that idea, but I have not seen any figures quoted.

Behnke The Indians are also exposed to cold in Peru. In the days of the Incas it was said — and this must be conjecture — that they were lightly clothed, and that their body temperature at night fell two to three degrees. Perhaps this is one of the reasons that they worshiped the sun. They were glad to see the sun

Talbott You appreciate that Peru is only a short distance from the equator The determining en ironmental factor so far as temperature is concerned, in the mountains is altitude Having spent several months there I would not say that the temperatures varied appreciably from those at Leadville, Colorado at 10,000 feet where it gets colder in the winter time than it does in Chile and Peru

Behnke Ten and 12,000?

Talbott Fourteen and 18,000 feet

Behnke To get back to this matter of acclimatization Has anyone really studied people who are supposedly acclimatized to cold? I refer to Patagonians who run around with few clothes and who are cold What do we know about people whose bodies are exposed habitually to extreme cold?

Kark As far as I could find only the most superficial stud es have been made on Eskimos. Very little is known about the Patagonians, except anthropological studies made by the people in the Argentine.

Horvath Hicks has done some work on the Australian aborigines, too which must be kept in mind

Behnke Yes, but the Eskimo does not get cold. Their clothing is a little bit better than what we have been able to produce until recent years They keep warm. But the Patagonians are exposed to the cold, and wear only meager clothing

Barton There are not too many Patagonians left to study

Edholm No the majority have died

Behnke Probably it is because they have become sterile.

Edholm No, they died of measles.

Talbott Colonel Blair didn t you have something to say on this subject?

Blair Yes, chiefly on cold acclimatization in animals

At the Army Medical Research Laboratory a group of us have been very interested in the cold acclimatization problem We have been study ing various aspects of cold acclimatization in animals, particularly physiologically induced resistance to cold injury

The experimental data that I wish to present at this time are not intended merely to introduce new material, but rather to point out, first, some very pertinent research problems associated with cold acclimatization and second some interesting research leads for further study and evaluation.

I shall not go into details as to the techniques used in the cold acclimatization of our animals The following abstract gives the conditions, duration of exposure, and ambient temperatures at which the rabbits and rats were cold acclimatized

Acquired resistance to cold exposure in the rabbit and the rat. J R. Blair, J M. Dimitroff and J E Hingley (Introduced by A. D Keller) Army Medical Service Field Research Lab., Fort Knox, Kentucky

Groups of 6 rabbits and 12 rats were conditioned to moderate cold exposure for a 7 week period. The rabbits were housed for 20 hours of each day in an ambient temperature of −20 F (−29 C.) while the rats were housed 16 hours daily at 20 F (−7 C.) The foregoing ambient temperatures have proved to be the lower range of cold exposure which each of these species, when not previously conditioned to cold, can tolerate w thout adverse physiological reactions At the end of the 7 week conditioning period to moderate cold, these groups of animals, along with similar control groups, were exposed to a more severe degree of cold. The rabbits were exposed for an 8-hour period to an ambient temperature of −50 F (−45 C.) and the rats for 5 hours at 5 F (−15 C.) The cold-conditioned animals, without exception, tolerated the period of exposure to severe cold without adverse physiologic responses namely hypothermia and cold injury (frost bite) On the othe hand all unconditioned animals suffered progressive hypothermia and second- or third-degree frostbite. These observations are interpreted as demonstrating (1) that rabbits and rats, under appropriate conditioning to moderate cold, acquire an unusual resistance to severe cold exposure, and (2) that these two species have different quantitative physiological tolerances to cold exposure (36)

The experimental animals (rabbits and rats) were chosen because they could be very carefully selected and controlled from standpoint of strain, age, sex, size, and weight. Such is not true of dogs and cats, as usually acquired from pounds and without special breeding

Let us first consider the effect of cold acclimatization upon the animals ability to maintain a constant internal temperature, or to prevent development of hypothermia when exposed to extreme cold. Table III shows the colonic temperatures before and after five hours exposure at 5 F of twelve normal (nonacclimatized) rats and twelve rats which had been acclimatized over a period of seven weeks at an ambient temperature of 20 F During this seven week acclimatization period the nonacclimatized rats had lived at an ambient temperature of 77 F Examination of the data reveals that all nonacclimatized rats suffered a moderate to severe

TABLE III

Colonic Temperatures of Rats Before and After 5 Hours Exposure at 5 F

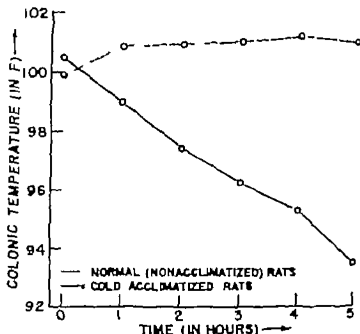
Normal (Nonacclimatized) Rats				Cold-Acclimatized Rats			
Rat No.	Before Exposure	After Exposure	Change	Rat No.	Before Exposure	After Exposure	Change
9-A	99.8	96 4	−3 4	1 B	101 0	101	+0 2
10-A	101.0	93.0	−8 0	2 A	99 4	101 5	+2.1
10-B	100.8	88 9	−11 9	2 B	100 1	99 7	−0 4
11 A	100.0	86 7	−13 3	3-A	99 5	102.2	+2 7
11 B	99 6	93 7	−5 9	17 A	99 6	100 3	+0 7
12 A	100 2	97 3	−2 9	17 B	98 3	99 3	+1.0
12 B	100 7	91 5	−6 2	18-A	99 8	101 5	+1 7
13 A	101 0	92 9	−8 1	18-B	99 1	100 7	+1 6
13-B	101 3	91.0	−10 3	19-A	99 0	101 4	+2.4
15-A	100 0	94.0	−6 0	19-B	101 2	101 8	+0.6
15-B	101 0	97 0	−4 0	20-A	100 8	101 8	+1.0
16-B	101.0	97 4	−3 6	20-B	101	101 6	+0 4
Average	100 5	93 5	−7 0	Average	99 9	101 1	+1.2

(All data expressed in degrees Fahrenheit)

fall in internal temperature, averaging 7 F whereas all cold-acclimatized rats with one exception, showed an increase in internal temperature, with an average rise of 1.2 degrees Table IV shows a graph of the

TABLE IV

Mean Colonic Temperatures of Rats During 5 Hours Exposure at 5 F



mean colonic temperature taken hourly during five hours exposure at 5 F first, of twelve nonacclimatized rats, and second, of twelve rats which had been previously cold acclimatized over a seven-week period. The mean colonic temperature of the cold-acclimatized rats (broken line) steadily rises throughout the five hour exposure period whereas the nonacclimatized rats internal temperature (solid line) shows an uninterrupted progressive fall into a state of hypothermia

Gottschalk Was there any gross difference in the degree of activity of the rats?

Blair No I shall discuss that point later but there was no difference in activity of the two groups that we were able to detect.

Horvath Did they huddle up more?

Blair No they were identical, as far as we could see, in their behavior in the cold. Only one animal was kept in each cage.

TABLE V

Colonic Temperatures of Rabbits Before and After 8 Hours Exposure at −50 F

Normal (Nonacclimatized) Rats				Cold-Acclimatized Rats			
Rabbit No	Before Exposure	After Exposure	Change	Rabbit No	Before Exposure	After Exposure	Change
2 F	101.6	99 2	−5 4	2 B	10 2	102 5	+0 3
2 J	103 5	96.2	−7 3	2 H	102 7	100 5	−2.2
2 K	103 4	101 2	−2 2	2 M	101 9	103 6	+1 7
3-B	103 9	96 7	−7.2	3-A	103 8	102 6	−1 2
3-G	102.9	101 8	−1 1	3-F	103 2	103 3	+0 1
3-L	103 6	97.2	−6 4	3-H	102 9	103 4	+0 5
Average	103 7	98 7	−5 0	Average	102 8	102 7	−0 1

(All data expressed in degrees Fahrenheit)

Kark What happens if you take animals under a barbiturate anesthetic and put them in the cold?

Blair We have not done that. It would be a very interesting observation to make

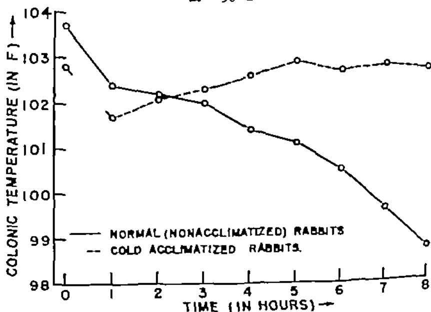
Sellers We have done that. Our work is quite similar

Blair When we get into the discussion of these research problems on cold acclimatization, Dr Sellers will be able to contribute a great deal, because he has carried out a large number of very similar studies.

Let us now examine similar studies carried out on rabbits. Table V shows the colonic temperatures before and after eight hours exposure at −50 F of six normal (nonacclimatized) rabbits and six rabbits which had been previously acclimatized over a period of seven weeks at an ambient temperature of −20 F No ill effects were experienced by any of the rabbits during or after cold acclimatization. During this seven week acclimatization period the nonacclimatized rabbits lived in an ambient temperature of 77 F The cold acclimatized rabbits were able to maintain a relatively constant internal temperature as compared to the nonacclimatized rabbits, all of whom showed a fall in colonic temperature, averaging 5 F The curves shown in Table VI demonstrate the ability of

TABLE VI

Mean Colonic Temperatures of Rabbits During 8 Hours Exposure at −50 F



cold-acclimatized rabbits (broken line) to maintain a normal internal temperature throughout eight hours exposure at −50 F On the other hand, nonacclimatized rabbits (solid line) like the nonacclimatized rats, experience a progressive decrease in mean colonic temperature. It is interesting that in the first hour of exposure both groups of rabbits behaved almost identically with one-degree fall in colonic temperature

Table VII presents similar data of cold injury experienced by six nonacclimatized rabbits and six cold acclimatized rabbits after eight hours exposure at −50 F All nonacclimatized rabbits developed moderate to severe frostbite of the ears and, to a lesser degree, of the feet and tails. The only frostbite present among the cold acclimatized rabbits was ery mild first-degree involvement of one ear of one rabbit. These data are in direct confirmation of that already presented for rats Figures 36 and 37 show photographs of the ears of four nonacclimatized and four cold-acclimatized rabbits taken two days after eight hours exposure at −50 F The ears of the animals previously conditioned to cold remained normal dur ing and after cold exposure The ears of the nonacclimatized rabbits reveal typical third-degree frostbite with bleb formation ulceration, and gangrene. Close examination of the photographs with location of the line of demarcation reveals each ear to be appro imately three-fourths involved by gangrene.

These observations are interpreted as demonstrating that rats and rabbits, under appropriate cond tioning to moderate cold, acquire an unusual resistance to development of old injury when subjected to a more severe cold stress

At the present time we are most interested in what physiological changes occur during the acclimatization process to bring about this unusual resistance to the pathological effects f cold exposure Such a fall in internal temperature brings it to action in both groups of rabbits vari ous defense mechanisms against cold (shi ering vascular responses, metabolic changes and so forth) In nonacclimatized rabbits all these defense mechanisms are able to do s is briefly slow down the fall in colonic temperature but in cold-acclimatized a imals they are sufficient to bring the internal temperature back to normal and maintain it indefinitely at a normal level

The second criterion used as evidence of old acclimatization was the animals ability to withstand development of cold njury when exposed to extreme cold. In Table VIII one may observ the extensive cold injury present in nonacclimatized rats after five hours exposure at 5 F With only one exception all rats not previously conditioned to cold suffered second (blistering) or third-degree (gangrene) frostbite of their tails. Only in one of the previously cold-acclimatized rats was there a suggestion, a reddening of the tip of the tail that disappeared within

TABLE VII

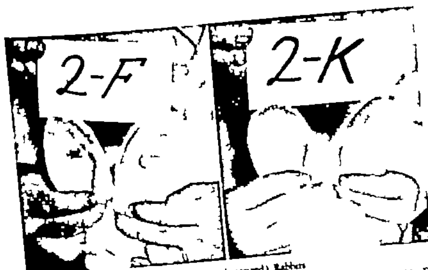
Cold Injury of Rabbits After 8 Hours Exposure at −50 F

Normal (Nonacclimatized) Rats				Cold-Acclimatized Rats			
Rabbit No.	Cold Injury Ears	Cold Injury Feet	Cold Injury Tail	Rabbit No.	Cold Injury Ears	Cold Injury Feet	Cold Injury Tail
2 F	+++	++	++	2 B	0	0	0
2 J	+++	++	++	2 H	+	0	0
2 K	+++	0	+	2 M	0	0	0
3-B	+++	++	++	3-A	0	0	0
3-G	++	0	0	3-F	0	0	0
3-L	+++	+	++	3-H	0	0	0

+ = First-degree frostbite (erythema and swelling)
++ = Second-degree frostbite (blistering and fissuring)
+++ = Third-degree frostbite (gangrene and tissue loss)

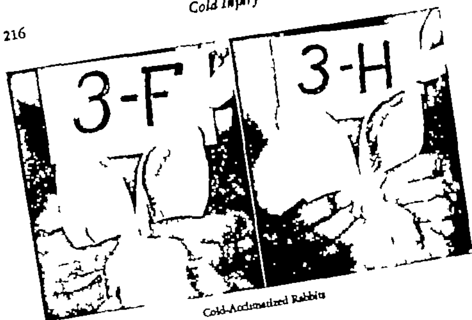


Cold Acclimatized Rabbits

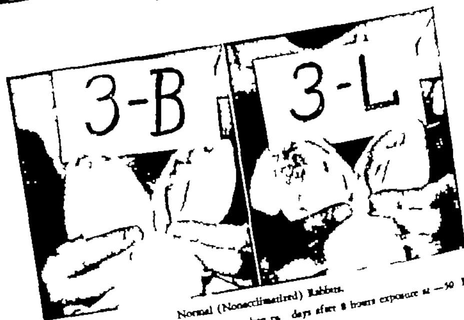


Normal (Nonacclimatized) Rabbits

Fig. 36 Photographs of rabbits' ears taken [illegible] days after 8 hours exposure at −30 F



Cold-Acclimatized Rabbits



Normal (Nonacclimatized) Rabbits.

FIGURE 3. Photographs of rabbits ears taken ra days after 8 hours exposure at —50 F

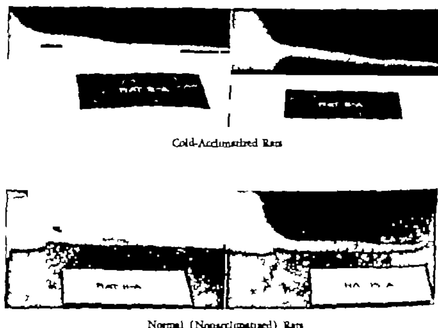
TABLE VIII

Cold Injury of Rats After 5 Hours Exposure at 5 F

Normal (Nonacclimatized) Rats				Cold-Acclimatized Rats			
Rat No.	Cold Injury Ears	Cold Injury Feet	Cold Injury Tail	Rat No.	Cold Injury Ears	Cold Injury Feet	Cold Injury Tail
9-A	0	0	+++	1 B	0	0	0
10-A	0	+	+++	2 A	0	0	0
10-B	+	+	+++	2 B	0	0	0
11 A	+	++	+++	3-A	0	0	0
11 B	0	+	+++	17 A	0	0	+
12 A	0	+	+++	17 B	0	0	0
12 B	0	0	++	18-A	0	0	0
13-A	0	+	++	18-B	0	0	0
13-B	+	+++	+++	19-A	0	0	0
15-A	0	+	+++	19-B	0	0	0
15-B	0	0	+	20-A	0	0	0
16-B	0	0	++	20-B	0	0	0

\+ = First-degree frostbite (erythema and swelling)
++ = Second-degree frostbite (blistering and fissuring)
+++ = Third-degree frostbite (gangrene and tissue loss)

forty-eight hours, of any cold injury It is very easy to see the marked difference in cold injury between the two groups and to observe how previous acclimatization to cold protects the animal against frostbite when exposed to more intense cold stress Figure 38 shows photographs of rats



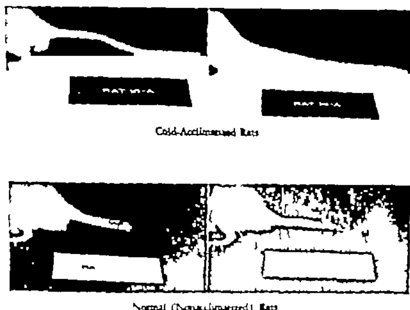
Cold-Acclimatized Rats

Normal (Nonacclimatized) Rats

FIGURE 38 Photographs of rats tails taken two days after 5 hours exposure at 5 F

tails taken two days after five hours exposure at 5 F The tails of the cold-acclimatized rats are entirely normal but those of the nonacclimatized rats are involved by third-degree frostbite with edema, swelling, ulceration, and gangrene. The prognosis of the latter is that seen in Figure 39 — mummification and sloughing of the tail at the line of demarcation. *The tails of all previously cold acclimatized rats are normal* We are now studying the phase of the problem from five different aspects (1) learning or behavior factor (2) metabolic factors, (3) increase in animal fur (insulation) (4) endocrine factors, and (5) circulatory adjustments.

Dr Horvath and Dr Gottschalk brought up what is certainly a very important factor in human beings, and that is, learning to live in the cold We know from experience in the Arctic that one of the most striking adaptations to cold is that man learns how to dress, how to use cold-



Cold-Acclimatized Rats

Normal (Nonacclimatized) Rats

FIGURE 59. Photographs of rats' tails taken tw k after hour exposure at 5° F.

weather equipment, and how to manage himself properly under conditions of cold stress. We have studied these animals very carefully through daily observations, and we could see no evidence of behavior changes either in rats or in rabbits. In every case the rabbits, both acclimatized and nonacclimatized, huddled into as small a ball as they could in the corner of the cage and shivered very vigorously with practically no voluntary activity. The rats behaved in a similar manner. As far as we were able to detect, from very careful visual observation, there was no learning factor involved in cold-acclimatization of rats and rabbits.

A second factor in cold acclimatization in which we are interested is that of increase in animal fur or pelt weight. It is a well-known fact that all fur-bearing animals have thick and heavy fur during the cold months of winter. This undoubtedly plays an important part in increasing animals' resistance to cold but is of no importance in human acclimatization. In all of our studies we have made comparative observations of the pelt weights of nonacclimatized and cold acclimatized animals. Such data is presented in Table IX. This table shows the weight of the pelts of nonacclimatized rabbits as compared to those of previously cold acclimatized

TABLE IX

Weight of Rabbit Pelts

Norma (Nonacclimatized) Rats				Cold-Acclimatized Rats			
Rabbit No.	Body Weight	Pelt Weight	% Body Weight	Rabbit No.	Body Weight	Pelt Weight	% Body Weight
2 F	3,294	366	11 1	2 B	2,785	455	16 3
2 J	2,954	328	11 1	2 H	2,116	342	16 1
2 K	3 598	330	9.2	2 M	3 101	442	14 3
3-B	3,399	372	10 9	3-A	2 749	329	12.0
3-G	3 592	416	11 5	3-F	3,269	390	12.0
3-L	3 101	405	13 0	3-H	3 601	425	11.8
Average	3,323	369	11 1	Average	2,937	397	13.6

(All data expressed in grams)

rabbits. The pelt weight consists of the weight of the skin plus the weight of the animal fur

An interesting thing to note in this study is that when we first began the acclimatization process, our rabbits were paired off — one experimental animal against one control, not only as to the same age and sex, but also identical body weight Although their caloric intake was approximately double, the cold-acclimatized rabbits experienced a slight fall in body weight, compared to a slight rise for the nonacclimatized This accounts for the small difference in final body weights of the two groups of animals in Table IX, averaging 3 323 grams for the control group against 2,937 grams for the experimental group

The pelt weight of the group of rabbits previously conditioned to cold averaged 397 grams or 13.6 per cent of total body weight. The average pelt weight of the nonacclimatized rabbits was 369 grams or 11 1 per cent of their total body weight We are continuing our studies on increased furring in cold acclimatization in order to learn how important a role it actually plays in increasing an animal s resistance to cold injury

Talbott Is the difference significant?

Blair Yes, the difference is significant, but we think it does not present the true picture. Most of this increase in pelt weight is due to increased fur and not increased skin weight. We have found it extremely difficult to remove all the hair from a rabbit and thus obtain the true fur weight But by feeling or measuring the depth of the fur the factor of increased insulation in cold acclimatization of animals becomes much more evident than when presented as an increase in pelt weight

Shumacker Colonel Blair if your two groups started out with identically the same weight, wouldn t it be more valid to compare the pelt weights with the original weights?

Blair We could just as well compare pelt weight with the animal s original weight, and t s true that it might be a more valid comparison

Sellers Colonel Blair was there actual weight loss?

Blair The food intake of the cold acclimatized rabbits averaged about twice of that of the nonacclimatized, but during the first week n the cold room their increase in caloric intake is quite small It requires one or two weeks in the cold to bring food consumption up to a constant maximum level It is during the first two weeks of cold exposure that the fall in body weight occurs. After this initial fall, they maintain their weight at a very constant level throughout the last five weeks of exposure On the other hand, the control rabbits, living at room temperature, eat at their normal rate and maintain a slight but steady increase in body weight.

Horvath Have you maintained the same two groups of animals on the same amount of food intake? For instance f the group in the cold was consuming, say a hundred calories and the other group outside was con-

suming 150 did you try to reduce the intake of the group outside to an equivalent amount, so that they had the same food stress?

Blair No we fed our animals only by placing before them five hundred grams of food daily At the end of the feeding period, we removed the food, weighed it, and finally calculated the grams of food eaten. We have not placed any of our animals either on a controlled diet or on a controlled amount of food.

Sellers Dr Horvath, there is a very interesting reason why that does not work with rats anyway and that is that they die If you give them their ordinary food intake at room temperature —

Horvath I was thinking primarily of the control group eating outside Do you have them eat the same amount of food as the ones in the cold, at least during that first week when you have your weight loss.

Sellers You would have to use a stomach tube

Horvath No you can feed them once a day That has been done repeatedly You can give it to them so that they eat all their food within a certain period of time and you can get them to eat that much

Sellers Well, under normal conditions, a rat won t eat thirty grams of chow per day unless he is a tremendous rat, but in the cold he eats thirty grams at the drop of a hat.

Horvath I realize they eat more I was interested more in that first week, when they eat less Isn t that what you said?

Sellers They eat more than the normal amount

Blair Yes they eat more than the control animals during the first week, but not nearly so much as they do during their last five weeks in the cold They never at any time eat less than the animals not in the cold.

Horvath May I ask one thing? Are those animals paired? Is that rabbit 2F say your control for 2B? Is that why you have them in those lines?

Blair No the controls are not paired alongside the experimental animals both groups are simply arranged in alphabetical order — 2F 2J 2K, and so forth

Horvath There is an animal of body weight 209 with a pelt weight of 328 another animal with a body weight of 228 and a pelt weight of 329 You can go through that group and make some matches of various weights They look very much alike for the weights

Blair Yes, some of them you can match up very well but they are not arranged in any matched fashion in the table presented. It would be easy to go back to our original basic data and arrange them in a table, cold-acclimatized animal alongside its corresponding nonacclimatized control

A second factor in acclimatization to cold may be metabolic changes. The observation that animals in the cold do not increase in weight with

approximately doubled food intake certainly suggests that there is increased metabolic activity in cold acclimatized animals during the period in which they are cold-exposed The next question that arises is this When both groups of animals, the nonacclimatized and the cold acclimatized, are put under a severe cold stress, what is the heat production in those which are cold acclimatized as compared to those which are not Right now we are in a kind of dilemma as to how to set up an animal calorimeter to measure heat production in rabbits at −50 F It may be quite difficult technically We hope to obtain direct measurements of heat production soon but at present we do have some suggestive evidence that cold-acclimatized animals maintain a higher metabolic rate during the period of severe cold stress than do the nonacclimatized

Tables X and XI list the weights of rats and rabbits taken before and after a period of severe cold exposure In order that all animals were at the same basal level food was withdrawn twelve hours before beginning the exposure. No food or water was given the animals while in the cold room. All rats and rabbits were weighed carefully just before and immediately after cold exposure. Weight loss has been expressed both as total grams and as per cent of body weight. Careful observation of the two tables reveals that weight loss in cold-acclimatized animals was much greater than that in nonacclimatized controls — 9 3 per cent of body weight compared to 4 8 per cent in rats, and 8 8 per cent compared to 6.0 per cent of the body weight of rabbits. We feel that this greater loss of body weight by cold acclimatized animals during exposure to severe cold may be due to their greater utilization (metabolism) of body materials for heat production in order to maintain body temperature and prevent development of cold injury

One question that we are unable to answer at present is whether the acclimatized animals are able to step up and maintain their metabolism at a higher level in the cold than are the nonacclimatized or whether both groups begin the cold exposure at the same metabolic level, with the metabolic rate of the nonacclimatized gradually falling off resulting in hypothermia and cold injury

Horvath Do they produce more urine, by the way — the nonacclimatized group

Blair During the acclimatization period?

Horvath No I mean in this test period

Blair I do not have figures available on that, but in this test period there appears to be very little difference However during the acclimatization phase the animals in the cold drink and urinate considerably more water than the controls at room temperature

Horvath Apparently an animal which is used to the cold and an animal which is not used to the cold put out the same amount of urine

TABLE X

Weight of Rats Before and After 5 Hours Exposure in Cold Room at 5 F

Normal (Nonacclimatized) Rats					Cold-Acclimatized Rats				
Rat No	Before Exposure	After Exposure	Weight Loss	% Loss	Rat No.	Before Exposure	After Exposure	Weight Loss	% Loss
9-A	426	394	32	7 5	1 B	350	303	47	13 4
10-A	438	424	14	3.2	2 A	432	390	42	9 7
10-B	393	377	16	4.1	2 B	428	396	32	7 5
11 A	360	345	15	4.2	3-A	465	432	33	7 1
11 B	429	410	19	4 4	17 A	378	337	41	10.8
12 A	417	392	25	5 9	17 B	348	310	38	10 9
12 B	444	422	22	4 9	18-A	320	290	30	9 4
13-A	423	405	18	4.2	18-B	382	348	34	8 9
13-B	428	408	20	4 7	19-A	428	393	35	8.2
15-A	422	405	17	4.0	19-B	358	324	34	9 5
15 B	434	414	20	4.6	0-A	339	316	23	6 8
16-B	404	380	24	5 9	20-B	314	286	28	8 9
Average	418	398	20	4 8	Average	379	344	35	9 3

(All data expressed in grams)

TABLE XI

Weight of Rabbits Before and After 8 Hours Exposure in Cold Room at −50 F

Normal (Nonacclimatized) Rats					Cold-Acclimatized Rats				
Rabbit No	Before Exposure	After Exposure	Weight Loss	% Loss	Rabbit No	Before Exposure	After Exposure	Weight Loss	% Loss
2 F	3 294	3 058	236	7 2	2 B	2,785	2,505	280	10 1
2 J	2,954	2,755	199	6 7	2 H	2,116	1,894	222	10 5
2 K	3 598	3,356	242	6 7	2 M	3 101	2,844	257	8 3
3-B	3 399	3,237	162	4.8	3-A	2,74[illegible]	2,488	261	9 5
3-G	3 592	3 408	184	5 1	3-F	3 69	3,016	253	7.8
3-L	3 101	[illegible],925	176	5 7	3-H	3,601	3,331	270	7 5
Average	3 323	3 123	200	6 0	Average	937	2,680	257	8.8

(All data expressed grams)

Blair As far as we can see, but based only on just one severe cold exposure.

Burton These weight losses then represent insensible water loss plus the CO_2-oxygen metabolic loss, and nothing else?

Blair That is correct metabolic loss and insensible water loss from the lungs and skin The latter may be quite large in the cold room at subzero temperatures where the absolute humidity is always very low

Gottschalk It would be interesting to compare the weight loss with the pulmonary ventilation rate

Kark Yes I was going to ask you, have you done any tissue analyses in these animals?

Blair No that is something that we have never done

One of the most interesting aspects of this cold acclimatization study is that increased fur and increased metabolism must play only a minor part in protecting from cold injury the tails and ears of cold acclimatized rats and rabbits In both of these structures no one can observe any increase in fur or insulation as a result of acclimatization. Likewise the acclimatized animal does not learn to protect the tail or ear by burying it in his body fur Often but not always the tail or ear will begin to freeze before there is any fall in the animal s colonic temperature Thus there appear to be factors other than learning, fur growth, or metabolism concerned in protection of tails and ears of animals against frostbite. There are several possibilities One already mentioned is circulatory changes, such as strengthening or conditioning the hunting reaction, to provide local protection against cold injury Another possibility is that preconditioning to cold may increase a tissue s resistance to freezing or cold injury And a third possibility — perhaps Dr Crismon can give us some information on this — are acclimatized tissues able to step up their metabolism to a higher level than nonacclimatized tissues? In other words, Dr Crismon, are there any Warburg tissue slice technique studies on oxygen consumption in cold acclimatized as compared to nonacclimatized tissue?

Crismon I did not know of any on animals until Dr Sellers handed me this one.

Talbott Why don t you tell us about your studies, Dr Sellers?

Sellers Of course I have been extremely interested in this last presentation, first of all because of its excellence, and second, because it is complementary to our experiments In fact, if the experiments had been designed to be complementary I don t think they could have been arranged better

Well, although our approach has been somewhat different, a good many of the facts demonstrated are exactly the same (31 32 37 38 39 40 41) About a year and a half or two years ago we decided that it

would be an interesting procedure to shave rats and expose them t a temperature of just above freezing, which temperature we have used ... istently We found that if rats were shaved and placed in our cold ... m they would die invariably within twenty-four hours. We then to... a that were accustomed to living in the cold environment, that is they ... been in it for more than six weeks, and clipped them as close as p... with an electric clipper and exposed them to the same temper... To our surprise, they lived on quite satisfactorily for many weeks ... n ... cases until the fur had grown back in.

The next procedure was to find out why they were living, so we m... ured the oxygen consumption of the rats in the cold room We found that in the case of acclimatized clipped rats, and also in nonacclimat... clipped controls there was an immediate increase in oxygen consump tion to a level that we had not encountered before The usual rate with our method, recording at 30 for a normal rat is about 130 cc. of ... per per square meter body surface per minute In the cold these clipped animals sometimes used as much as 500 cc. per square meter per minut If we followed the oxygen consumption every few hours, we soon found that the acclimatized clipped animals continued to produce heat (use oxygen) as long as we cared to observe them (which was for a numbe of weeks) but that the oxygen consumption of the nonacclimatized con trols fell off quite quickly and that the animals were dead by the foll w ing morning.

The comparison of the oxygen consumption at 1.5 C of the acclimatized animals with and without their fur was that the clipped rats showed a 50 per cent increase in oxygen consumption above the already greatly elevated rate caused by the low temperature. The way that they maintained their body temperature was to increase their heat production

The question then came up How are they producing the increased amount of heat? The most obvious suggestion was by means of muscular activity and here we were impressed by the observation of Burton and Bronk (42) made some years ago that it was not necessary to have obvious shivering to have increased muscular activity

We anesthetized animals, using sodium pentobarbital in doses small enough to maintain anesthesia for an hour and a half which was the period that the animals remained in the oxygen measuring apparatus. We found that the fall in oxygen consumption was very great indeed. In the clipped animals, as compared to the nonclipped animals, there was another interesting difference in that apparently the heat loss was too great to be consistent with survival so that after anesthesia the clipped animals died, and the nonclipped were able to survive this period of anesthesia in the cold.

Gottschalk May I interrupt a minute? What happens to the oxygen consumption following anesthesia if the rabbits are kept at what for them is a comfortable temperature?

Sellers That is an interesting point. If the animals are kept in the cold but the oxygen-consumption measurements are taken at 30° the oxygen consumption is increased by about 30 to 50 per cent above the normal level This is true both of the acclimatized and of the nonacclimatized animals so from that fact that the basal metabolism as recorded at 30 is the same in the two types of animals we believe that most of the increase is due to increased muscular activity

However we have been interested in tissue metabolism for a long time —

Shumacker Pardon me, Dr Sellers, but did you finish with regard to the anesthetized animals? Did both the acclimatized and nonacclimatized animals die if they were shaved and anesthetized?

Sellers They would both die yes

Horvath About fifteen years ago when we were working on this problem of relationship to cold and adrenalectomy we had the opportunity to study some hairless rats.

Kark Where did you get them?

Horvath They were mutants at the University of Illinois. I think there are still some there Dr Roberts still has them.

Kark I have been looking for those for a long time

Horvath When you exposed these hairless rats to cold, they would die within a very short time, whereas the ones with hair even though they had not been exposed to the cold previously would do fairly well

I don t recall anything about the histology of the skin of these animals, but might they not have lost the mechanism which would result in pilomotor activity and therefore be associated with some other factors of tremor? On the basis of that and the work which Dr Burton has done, I wondered whether or not that is the reason they failed The clipped rats, on the other hand although they had lost their pelt, still had the ability to shiver maintaining pilomotor activity and other mechanisms of increasing muscular tone

Crismon Dr Sellers, did you notice any differences in their ventilation rate?

Sellers We did not measure respiratory quotients, and general observation agrees with the remarks with which Dr Fremont Smith opened the Conference namely that in the cold, there is an increased rate and depth of respiration We have not made any specific observations on respiration

Crismon No difference between the two?

Sellers Not that I have observed.

Cranow There is an important relationship between resp at ority and shivering, apparently connected through the bulba t l centers. I have noticed that in animals that are hypotherm h t shivering often coincide with the inspiratory phase

Sellers That is very interesting We have done much to l t l measurements of muscle activity and we intend to proceed w

But to revert to Dr Gottschalk s question as regards the basal rate, that is, the metabolic rate measured at 30 I mention l was a 30 to 50 per cent increase in this rate when the val es t exposed to cold are recorded That suggested to us th n tissue might be contributing to this increase So Dr R ver u of my associates, carried out tissue respiration stud es l apparatus, and found there was a significant increa e in th sumption of liver slices amounting to about 20 per cent hese ments, and an even more significant and dramatic incre se t dioxidase activity of liver tissue homogenates when ti sue r acclimatized animals were compared with normal contr ls

We then wanted to study the process of acclimatization n gre t tail how long did it take to be produced and how long did t la t the animals were removed from the cold?

The procedure followed was to use the same test that f exp clipped animals to an environment of 1 5 or 2 C The anim ils w their normal complement of fur were placed in the col l room for ing periods of time varying from one day to six weeks Then they w removed from the cold room, shaved, and after they had recovered from the anesthetic which we gave to facilitate shaving we repla ed them in the cold room.

As far as we can say there is little or no acclimatization before tw to three weeks, and the acclimatization under these conditions appeared to be complete at about five to six weeks.

When acclimatized animals were removed from the cold room and were kept for varying periods of time at normal temperatures, were shaved, and then replaced in the cold room, they lost some of their ability to survive in as short a time as four days There was still a significant degree of acclimatization at four days.

Fremont Smith Was consumption back to normal then?

Sellers We have not done that sir

Blair I might mention, in relation to the work reported by Dr Sellers, that we have also studied the rate of development and loss of cold acclimatization in the rat. It is very interesting that our results on development of acclimatization correspond almost exactly with his. And our rea son for accepting seven weeks' exposure to cold as our standard acclima tization period was the observation that it required approximately six or

seven weeks to develop maximum acclimatization in animals. However on the rate of loss of acclimatization — Dr Sellers used a different technique for measuring loss of acclimatization — we find that our results do not follow quite the same pattern. We have used as our criterion of maintenance of acclimatization the rate at which acclimatized rats internal temperature falls on being subjected to extreme cold exposure, or the cold stress test which has been described previously You will recall from Table IV that the cold acclimatized rats maintained a normal internal temperature throughout the cold stress period, whereas the nonacclimatized animals showed a definite and constant rate of fall. Using this observation as our criterion of cold acclimatization, we repeated the test on the acclimatized rats one, two three, and four weeks after acclimatization. We found that their performance after one week was in the vicinity of about 75 per cent as good as immediately after acclimatization So we concluded that they had lost a quarter of their ability to resist cold. After about two weeks the rate of fall in colonic temperature was approximately midway between their ability to maintain a constant temperature and the steady rate of fall that you see in nonacclimatized rats Most of the acclimatization had disappeared, but one could always see some evidence of it after four weeks That is as long after acclimatization as we have studied our rats Thus, we conclude that about 25 per cent of the resistance to cold is lost for each one week period at room temperature: 25 per cent, 50 per cent, 75 per cent, and almost a total loss one two three, and four weeks following cold acclimatization.

Sellers That test is much more sensitive and is probably preferable to ours, which is a pretty severe test of increased resistance.

Just to finish off there are twenty or more details in which our experiments agree completely with yours, and practically none, where the conditions are relatively the same where they disagree.

Blair That is right

Sellers I am extremely interested in that fact

To sum up then, in a sentence or two what our view is as to the difference between acclimatized and nonacclimatized animals, we feel that the ability to continue producing a very large amount of heat is the essential difference. The acclimatized animal continues the production for a long time the nonacclimatized animal cannot do this We attempted to produce some of these changes artificially by using various chemical and hormonal substances We used the ones that you would expect we would use The only combination that we found satisfactory was giving cortisone with thyroxin for a period of at least a week before exposure to cold Either of those substances given singly in the doses and the regimen we used did not appear to be effective.

Talbott How much were you able to increase the surv[illegible] those that you did so prepare?

Sellers Well half as much as the increase in the natura lly [illegible] animals.

Talbott You were able to achieve 50 per cent accl ma[illegible] week's preparation?

Sellers Roughly that is correct.

Barton I might add to what Dr Sellers has said [illegible] scem[illegible] phenomenon which the two of us heard about at a confe[illegible] Canada, from Dr Campbell in Toronto but which n[illegible] related. Dr Campbell is a biochemist who has been in[illegible] with anterior pituitary extract I think it is crude extra[illegible] periods of time, he kills the animals and does a li[illegible] the slices and he has found a remarkably progress ve[illegible] metabolism following the injection of this anterior pitu[illegible] That appears to tie in with what Dr Sellers has found

Crismon Dr John Field became interested in some obser[illegible] polar cod, whose normal habitat temperature is −1 5 C (43) [illegible] taken from that animal show a much higher level of oxygen consu[illegible] than do comparable tissues taken from Temperate Zone fishes Th[illegible]ing hypothesis was that perhaps these animals ha[illegible]e become adap[illegible] the cold environment through some property within their [illegible]ell enables them to produce a higher concentration of enzymes It m[illegible] that if these fishes were kept in warmer water for a long time they w[illegible]ld assume levels of oxygen consumption comparable t[illegible] those of Tempe[illegible]ate Zone fishes. Conversely Temperate Zone fishes might be able to underg[illegible] some adaptation to cold

The differences that appeared at first between the measurement o[illegible] polar cod and the golden orfe, a Temperate Zone fish decreased markedly when we changed over to measurements on another polar fish the sculpin. Those two animals come from the same environment from the standpoint of temperature and yet the differences between the more sessile form the sculpin, and the other polar fish the cod were just as great as the initial differences between the active polar cod and the active golden orfe at Temperate Zone environment

Horvath I was rather interested in this problem of seven weeks to get acclimatized, which I put in quotes because it goes back to another Macy conference on problems of aging Using a relative ratio of aging between rats and man that would imply that it would take some five years of a high metabolic rate of three times basal for a man to become acclimatized to cold.

But the question I want to get back to is one Dr Kark brought out

initially Since you are working on acclimatization you might give a definition of what you mean by acclimatization, starting with Dr Sellers and then going to Dr Blair and anybody else who would like to give us a definition of acclimatization to cold, keeping in mind that seven weeks in the rat are equivalent to five years in the man s life

Fremont Sm th Or seventy

Horvath Yes I will qualify that Dr Fremont Smith

Siple Not to take a crack at the definition, I would say from practical experience we come to the figure of twenty two weeks, with no laboratory evidence

Horvath In man?

S ple In man there was a change particularly when you suddenly transported a man from tropical conditions to Arctic conditions We also observed that as temperatures continued to fall, we were not approaching that acclimatization and therefore we would start in from a summer period We noticed a little difference after two weeks and then very little difference until we had gone clear through a polar winter night, and then the temperature started back. When we got back to a temperature like −20 which had been severe when we first encountered it, it seemed almost mild. We felt it was comfortable by comparison with the −60°s that we had had for a couple of months in a row In other words, there is something there that is observable from a very gross standpoint.

Fremont Smith Isn t it perfectly reasonable to suppose that there are variations in adaptation to such a particular thing as cold in different species of animals of the same life span?

Kark And in different people

Fr mont Sm t Yes, I will come to that. And therefore you would not expect to be able to translate from one animal to man by just extending the life span there will be differences in different people.

Barton I would like to remind Dr Horvath that the action of hormones in small animals, as to the time relations, bear no relation to this ratio of physiological processes such as gestation. Thyroid takes very little less time to work in a rat — thyroid extract, thyroxin — than it does in man isn t that true?

Horvath That is exactly right. I was just trying to point out that very interesting possibility having to wait such a long period of time If you want to extend it to its most ridiculous end you might say that ten days for a rat is equivalent to one year for a man.

Talbott This discussion could be continued for some little time, but we are beginning to lose members of our group to airline and rail transportation.

I should like to make two points in closing Dr Frank Fremont Smith would welcome any suggestions from the participants regarding the con-

duct of these conferences. Even though they have been conducted for some twelve or fourteen years they are still in the experimental stage. If you have any suggestions, I recommend that you write to him. Secondly we did not have time to discuss research projects in the cold-injury field. I will appreciate it if you will send on any suggestions when you return your edited comments.

Fremont Smith Send us any ideas concerning areas which should be investigated and which you think particularly demand study at this time, whether or not your own laboratory can undertake them I think that we might stimulate somebody else to do that research This is Captain Behnke's suggestion

Talbott I wish to take this opportunity to thank the Josiah Macy Jr Foundation, and particularly Dr Fremont Smith, for making this Conference possible I also want to thank each of you for participating and giving up your responsibilities for this period of time in order to come to the Conference. To those of you who come from other countries and from foreign lands, my particular thanks

We shall assemble again next year

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